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EXPERIMENTAL AND CLINICAL STUDIES

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PSYCHOSOMATIC MEDICINE
EXPERIMENTAL AND CLINICAL STUDIES

Published quarterly (on a cooperative, non-profit, non-salary basis) with the sponsorship of the NATIONAL RESEARCH COUNCIL, Division of Anthropology and Psychology, Committee on Problems of Neurotic Behavior:—

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PURPOSE: The aim of PSYCHOSOMATIC MEDICINE, which has been initiated with the assistance of the Josiah Macy, Jr. Foundation, is to encourage and bring together studies which make a contribution to the understanding of the organism as a whole, in somatic and psychic aspects. These materials are now usually separated widely in manner and place of publication because of differences in concept, approach and methods. The inauguration of this journal will provide a channel for the prompt and inexpensive publication of relevant investigations. (See inside back cover for explanatory note.)

SCOPE: The investigations published in this journal will deal primarily with phenomena observed concurrently from somatic and psychic angles rather than from either one alone. The scope therefore will include appropriate experimental studies of animal and human behavior, and well-controlled clinical studies of both children and adults. Pertinent examples are: investigations of experimental neuroses, of frustration, of physiological changes accompanying emotion, of vegetative and hormonal disturbances, and of psychiatric aspects of general and specific medical problems.

EACH NUMBER WILL INCLUDE A REVIEW OF RELEVANT LITERATURE IN THE FIELD OF ONE OR MORE OF THE MEDICAL AND RESEARCH SPECIALTIES.

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INTRODUCTORY STATEMENT

PSYCHOSOMATIC MEDICINE is an expression which has not yet obtained citizenship. It does not appear in the standard medical dictionaries. To physicians this expression will have various connotations. Like all new expressions, the term "psychosomatic medicine" may lead to misconceptions and misunderstanding unless a definition is provided. After such a definition has been clearly stated, the aim and the scope of this journal will be easily described if not self-evident.

Psychosomatic Medicine is not equivalent with what is understood by the term psychiatry. Psychiatry is concerned with the study and therapy of the disturbances of the mind whether these disturbances are the results of emotional experiences, or of anatomical changes (degenerative, inflammatory processes, or neoplasms) of the central nervous system. The principal interest of psychiatry is the diseased mind. Psychosomatic Medicine covers a different and broader field. Its object is to study in their interrelation the psychological and physiological aspects of all normal and abnormal bodily functions and thus to integrate somatic therapy and psychotherapy.

Psychosomatic Medicine is not restricted to any specific field of pathology. Medical specialties such as internal medicine, pediatrics, dermatology, opthalmology, etc., may be so restricted. Psychosomatic Medicine, however, is not a medical specialty of this kind; it designates a method of approach to the problems of etiology and therapy rather than a delimitation of the area. This principle may be applied in the same way in internal medicine, pediatrics, dermatology, neurology or psychiatry. The pathological phenomena that belong to these different fields should be studied from both the physiological and the psychological point of view. Briefly, psychosomatic medicine concerns itself with the psychological approach into general medicine.

The medical reader at this point may feel a justified skepticism. He may agree with the editors that theoretically speaking all pathological phenomena may have a psychological aspect and that it might well be desirable that they be investigated also from this less tangible, more esoteric point of view. He may feel, however, that new sciences and methods cannot be developed at a moment's notice, even though they may be very much needed. Reading the expression, "psychosomatic medicine", he may be reminded of scientific or philosophical writings, which were so common in the last century, devoted to new, theoretically postulated, scientific disciplines, such as for example Wundt's "Psychophysiologie" or "Völkerpsychologie". These books were devoted to scientific disciplines which were essentially nonexistent. They were a program for the future rather than a report of facts already known or theories already developed on the basis of observations. A malicious critic of much of the 19th century psychology and philosophy might have justifiably observed that the main occupation of psychologists and philosophers consisted in writing introductions to scientific disciplines that did not yet exist.

The editors of this journal do not consider that they are introducing a

new journal in a field that does not yet exist. There is much intensive and active work of this type going on in this and other countries. The medical profession has awakened to the necessity of studying systematically what is commonly referred to as the "art of medicine", the understanding and the therapeutic utilization of the psychic component in the disease process, and in the emotional relationship between physician and patient. This intensive interest and research in medical psychology is a symptom of a new orientation toward the problems of disease, in fact the sign of the beginning of a new era in etiological and therapeutic thought.

This journal is devoted not to the isolated problems of the diseased mind or the diseased body, but to the interrelationships between emotional life and bodily processes both normal and pathological. On the other hand, it is not concerned with the metaphysics of the body-mind problem. Emphasis is put on the thesis that there is no logical distinction between "mind and body", mental and physical. It is assumed that the complex neurophysiology of mood, instinct and intellect differs from other physiology in degree of complexity, but not in quality. Hence again divisions of medical disciplines into physiology, neurology, internal medicine, psychiatry and psychology may be convenient for academic administration, but biologically and philosophically these divisions have no validity. It takes for granted that psychic and somatic phenomena take place in the same biological system and are probably two aspects of the same process, that psychological phenomena should be studied in their psychological causality with intrinsically psychological methods and physiological phenomena in their physical causality with the methods of physics and chemistry.

In recent years an increasing number of observations have been made concerning the correlation of psychological and physiological processes in the human organism. The influence of specific emotional tensions upon physiological changes has been studied both clinically and experimentally as has the influence upon the emotional life of physiological (for example hormonal) changes. Such observations and systematic studies have been scattered through various medical periodicals—journals of psychiatry, internal medicine, endocrinology, neurology, dermatology, and pediatrics. In the interests of unity and of further progress this journal aims to correlate contributions from the special fields.

For the *internist*, psychosomatic investigations are of utmost importance in evaluating the so-called "functional" and "organic" elements in all illnesses, especially incipient illnesses and illnesses with a neurotic coloring. The internist, if he includes psychic factors in the range of his clinical observation, can shed much light on the etiology and treatment of some of the most baffling disease entities with which we have to deal. For the *pediatrician* the psychosomatic approach has a similar value; but his contribution to the problem itself may be even more significant because he is in a position to keep developmental records (including physiological and psychological correlations) throughout the most important decade in life.

Every *psychoanalyst*, is puzzled at one time or another by symptomatology which occurs in the course of the analysis of every patient and recognizes the need for more accurate information concerning the effect of the emotions upon visceral function. On the other hand, since he is working with the most precise of our medical methods in the psychological sphere, his observations

if scientifically controlled are of supreme importance. The significance of PSYCHOSOMATIC MEDICINE for the neurologist and psychiatrist needs no further comment.

Finally the *physiologist* as well as the student of comparative physiology is only too well aware of the difficulties created by psychic factors in experiments he would like to consider precise. The bodily changes associated with emotion and emotional expression are familiar through the works of Pavlov and Cannon and their associates, but the mechanisms underlying the changes are obscure although the need for clarifying them has been amply demonstrated.

Of course subdivisions of all these more comprehensive phases of medical and scientific practice and research have their special contributions. The fact that the Board of Editors is aware of the importance of their inclusion is shown in the personnel of the Journal's Advisory Board.

The characterization "experimental and clinical studies" on the title page may suggest to some readers the old distinction between the art of medicine and medical science. It is the purpose of the editors to adhere to a unitary conception of medicine as an experimental science, to introduce scientific precision into the "art". The experimenter in the medical sciences may be a clinician or a laboratory worker. When he experiments, he makes something happen the better to observe the conditions governing its occurrence. It is no longer necessary to defend the thesis that medicine is a biological science and that its facts are derived from the study of animals as well as of patients.

The editors believe that there is further need for a journal in this field because papers presenting data on psychosomatic medicine are usually long and it is often difficult to find for them a medium of publication. Occasionally short papers may be accepted but it is better that these should go to the general and special journals already established, so that the interest in psychosomatic problems will spread widely rather than become concentrated in a group. Occasionally an authoritative general paper may be accepted, but it is our policy to publish data from which the reader can draw conclusions, and to avoid papers which merely express opinions. Reviews of special subjects will appear from time to time and will be thoroughly documented. As a rule, abstracts to keep the reader in touch with the current literature will be brief, aiming to show quickly where information may be obtained, rather than to give information.

In brief then, psychosomatic medicine is both a special field and an integral part of every medical specialty. It is an essential approach to every medical specialty in so far as it is fundamental in all diagnosis and treatment. In recent years a well defined species of research worker has appeared devoting himself to the study of psychosomatic problems. These investigators may represent the most diverse medical specialties, yet they are joined together by common interest and approach. The main purpose of this journal is to serve as a forum for workers in a field which has become vital in current medical research and therapy.

THE EDITORS

PSYCHOSOMATIC MEDICINE—VOL. I, NO. I, JANUARY, 1939

PSYCHOLOGICAL ASPECTS OF MEDICINE

FRANZ ALEXANDER, M.D.*

I. HISTORICAL PERSPECTIVE

ONCE AGAIN, the patient as a human being with his worries, fears, hopes and despairs, as an indivisible whole and not only as the bearer of organs—of a diseased liver or stomach—is becoming the legitimate object of medical interest. In the last two decades increasing attention has been paid to the causative rôle of emotional factors in disease and a growing psychological orientation manifests itself among physicians. Some sound and conservative clinicians deem this a threat to the so arduously acquired scientific foundations of medicine, and authoritative voices warn the profession against this new "psychologism" as incompatible with medicine as a natural science. They would prefer that medical psychology should remain restricted to the field of medical art, to tact and intuition in handling the patient, as distinct from the scientific procedure of therapy proper, that is based on physics, chemistry, anatomy and physiology.

From an historical perspective, however, this psychological orientation is nothing but a revival of old prescientific views in a new and scientific form. It was not always that the care of the suffering man was divided between the priest and the physician. Once the healing functions, whether mental or physical, were united in one hand. Whatever the explanation of the healing power of the medicine man or of the evangelist or of the holy water of Lourdes might be, there is little doubt that they often had a spectacular curative effect upon the sick, in certain respects even a more fundamental effect than many of our drugs, which we can analyze chemically, and the pharmacological effects of which we know with great precision. This psychological portion of medicine survived only in a rudimentary form as medical art and bedside manner, carefully separated from the scientific aspects of therapy, and is considered mainly as the suggestive, reassuring influence of the physician upon his patient.

Modern scientific medical psychology is but an attempt to place medical art, the psychological effect of the physician upon the patient, on a scientific basis and to make it an integral part of therapy. There is little doubt that much of the therapeutic success of the healing profession, of the medicine man and of the priest as well as of the modern practitioner, has been due to the undefined emotional rapport between physician and patient. This psychological function of the physician however was perhaps never more disregarded than in the last century in which medicine became a genuine natural science based on the application of the principles of physics and chemistry to the living organism. The fundamental philosophical postulate of modern medicine is that the body and its function can be understood in terms of physical chemistry, that living organisms are physico-chemical machines and the ideal of the physician is to be-

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come an engineer of the body. The recognition of psychological forces, a psychological approach to the problems of life and disease, appears as a relapse back to the ignorance of the dark ages in which disease was considered as the work of the evil spirit and therapy was exorcism, the expelling of the demon from the diseased body. It is only natural that the new medicine based on laboratory experiments jealously defended its newly acquired scientific halo against such antiquated mystical concepts as those of psychology. Medicine, this newcomer of the natural sciences, in many respects assumed the typical attitude of the newcomer who wants to make one forget one's low origin by becoming more intolerant, exclusive and conservative than the genuine aristocrat. Medicine became most intolerant toward everything which might have reminded it of its spiritual and mystical past, at a time when the aristocrat of the natural sciences, its older brother, physics, was undergoing the most profound revolution of its fundamental concepts, questioning even the shibboleth of science, the general validity of determinism.

These remarks however are not intended to minimize the accomplishments of the laboratory period in medicine which represents the most brilliant phase of its history. The physico-chemical orientation characterised by the precise study of fine details is no doubt responsible for the great progress as displayed by modern bacteriology, surgery, and chemo-therapy and pharmacology. It belongs to the paradoxes of historical development that the greater the scientific merits of a method, or scientific principle, the greater will be their retarding influence in a later more advanced period of development. The inertia of the human mind makes it stick to the ideas and methods which have been proven of great value in the past even though their usefulness has already served its term. The development of the most exact of sciences, physics, is full of such examples. Progress in every field requires a reorientation and the introduction of new principles. These new principles although actually not always contradictory to the old ones nevertheless are often rejected, and must struggle for their recognition. The scientist in this respect is just as narrow-minded as the man on the street. The same physico-chemical orientation of the laboratory era to which medicine owes its greatest accomplishments has become on account of its one-sidedness an obstacle to further development. This new scientific laboratory era of medicine is characterised by its analytic attitude. Typical of this period was a specialized interest in detailed mechanisms, in the understanding of partial processes. The discovery of finer methods of observation, especially the microscope, disclosed a new microcosm in giving an unprecedented insight into the minute parts of the body. Accordingly in etiology, in the study of the causes of the diseases, the principal aim became the localisation of the disease. Ancient medicine was governed by the humoral theory according to which the fluids of the body were claimed as the carriers of the diseases. The gradual development of the methods of autopsy during the Renaissance made possible a precise study of the details of the human organism and thus led to more realistic but at the same time more localistic etiological concepts. Morgagni at the end of the 18th century claimed that particular organs such as the heart, the kidney, or the liver, were the seat of the diseases. With the introduction of the microscope the localisation of the disease became even more narrowed down: the cell became the seat of disease. No one was more responsible for this particularistic concept in medicine than Virchow to whom

pathology owes more than to anyone else. He declared that there are no general diseases, only diseases of the organs and of the cells. His great achievements in the field of pathology and his great authority made of cellular pathology a dogma, which has influenced medical thinking up to the present day. Virchow's influence upon etiological thought is the most classical example of the above-mentioned paradox of history. The greatest accomplishments of the past become later the greatest obstacles against further development. The discovery of histological changes in diseased organs by the help of the microscope became the universal pattern for etiology. The search for the causes of diseases long remained limited to attempts to discover local pathological changes in the tissues. The concept that such local anatomical changes are but the immediate cause, and themselves might be results of more general disturbances which develop as the effect of faulty functioning, overstress or even emotional factors had to be discovered later. The less particularistic humoral theory which became discredited when Virchow successfully defeated its last representative, Rokitansky, had to wait for its revival in the form of modern endocrinology.

Few have understood the essence of this phase of medical development better than Stephan Zweig (*5*), a layman. In his book, "Mental Healers", he says "Disease meant now no longer what happens to the whole man but what happens to his organs . . . And so the natural and original mission of the physician, the approach to disease as a whole changes into the smaller task of localising the ailment and identifying it and ascribing it to an already specified group of diseases . . . This unavoidable objectification and technicalization of therapy in the 19th century came to an extreme excess because between the physician and the patient became interpolated a third entirely mechanical thing, the apparatus. The penetrating, creative synthesizing grasp of the born physician became less and less necessary for diagnosis". . . .

Not less impressive is the statement of Dr. Alan Gregg (*3*), a man who views the past and future of medicine from a broad perspective. "The totality that is a human being has been divided for study into parts and systems; one cannot decry the method but one is not obliged to remain satisfied with its results alone. What brings and keeps our several organs and numerous functions in harmony and federation? And what has medicine to say of the facile separation of 'mind' from 'body'? What makes an individual what the word implies—not divided? The need for more knowledge here is of an excruciating obviousness. But more than mere need there is a foreshadowing of changes to come. Psychiatry is astir, neurophysiology is crescent, neurosurgery flourishes, and a star still hangs over the cradle of endocrinology . . . Contributions from other fields are to seek from psychology, cultural anthropology, sociology and philosophy as well as from chemistry and physics and internal medicine to resolve the dichotomy of mind and body left us by Descartes".

II. The Rôle of Modern Psychiatry in the Development of Medicine

It was reserved to the most neglected and least developed portion of medicine, to psychiatry, to introduce a new synthetic aspect into medicine. For a long time during the laboratory period, psychiatry remained a rather isolated domain which had little contact with the rest of medicine. It was concerned with the mentally diseased, a field in which the usually accepted methods of

medicine proved to be much less productive than in all other fields. The symptomatology of the mental disturbances unpleasantly differed from the disturbances of the body. Psychiatry had to deal with delusions, hallucinations and the disturbances of the emotional life. These symptoms did not permit even a description in the usual terms of medicine. Inflammation can be described in physical terms: swelling, increased temperature and definite changes in the cells observable under the microscope. Tuberculosis is diagnosed by definite changes in the afflicted tissues and the presence of well defined micro-organisms. The pathological mental functions however had to be described in psychological terms. Since the functions of the mind roughly could be connected with brain functions, the interest turned toward the histological study of the brain tissue of deceased psychotics and histopathology became the scientific basis of psychiatry. Unfortunately—or perhaps from the point of view of progress, fortunately—in most cases of even severe mental disturbances no constant pathological changes could be discovered in the brain. It was only natural that one hoped for light to come from a further advancement of the knowledge of the cellular physiology of the brain. Even though one could not find gross pathological changes in the brain one expected that with the progressive refinement of investigative methods one would be able to find that basis of psychological disturbances in the disturbed function of the brain cells. Theoretically, of course, the validity of this expectation is undebatable. A powerful re-enforcement of these hopes came from the discovery of the infectious nature of general paresis. Although there was still a big gap to be bridged between the tissue changes and the psychological symptoms of general paresis, a new hope arose from the understanding of mental disturbances on the basis of pathological anatomy of the brain. However, the next step toward the solution of the mysteries of the diseased mind came from another source, from the psychoanalysis of Sigmund Freud.

We have seen that clinical psychiatry tried to approach the problems of mental disturbances by the help of the microscope, and in this effort became disinterested in the very essence of its own field, in psychological phenomena. The solution of these problems required however another type of microscope, a psychological microscope. When medicine, this newest of all natural sciences, developed a definite distaste for the psychological aspect of the living organisms, it naturally transferred this attitude toward psychiatry which out of necessity had to deal with mental phenomena. Physicians felt instinctively that this was the weak spot where the old medieval demonology threatened to creep in again into medicine. Psychiatry with its psychological problems became the stepchild of medicine and was not considered as equal to the other fields but rather a foreign body threatening the purity of scientific medicine which has fully adopted the methods of physics and chemistry. Psychiatrists in self-defense made strenuous efforts to make the rest of their colleagues accept them as equals, and over-emphasized their non-psychological attitude. They did not want to be considered as mental healers but as physicians like the other specialists, engineers of the body. They refused even to take cognizance of the existence of psychic problems. Psychological symptoms were only considered in so far as they served for the classification of certain diseases as in the system of Kraepelin, but no attempt was made to study their meaning.

Life, however, is stronger than theories. There was the large number of

mental sufferers who did not profit from the laboratory studies of the scientists and wanted help. The severe cases, the psychotics, were considered generally beyond help. Being often apathetic, and deeply submerged in their ailment, they did not rebel against this disregard of their needs. But the even vaster group of milder cases, the psychoneurotics, who constitute probably the majority of all human sufferers, wanted help. One of the saddest anomalies of medical history developed. The physician whom these patients forced to listen to their psychological complaints, who was unable to understand and to handle these symptoms with his onesided laboratory equipment, began to dislike this type of neurotic patient. In order to hide his ignorance he refused to consider them as really sick and accused them of malingering. In order to defend their scientific aura physicians had developed a distaste for psychological facts and now they turned this distaste against their psychoneurotic patients. The psychoneurotic patient was regarded as a nuisance, and felt as a living accusation against the inadequacy of prevailing methods and dogmas.

The hysterical patient played a cruel joke on his physician, indeed. He developed nervous symptoms which seemingly did not follow the laws of anatomy and physiology. He developed bodily symptoms of the kind which did not correspond to the distribution of the nerves but to morbid ideas, thus demonstrating the superiority of the "mind" over the "body". In response the physician became impatient with the nervous sufferer and stubbornly refused to deal with his symptoms on a psychological level.

This was the situation in which the young Freud, influenced by Charcot's hypnosis experiments, decided to earn his living by giving real help to the psychoneurotic. For this purpose he felt he must understand the nature of the neuroses. The end-results of this endeavour were known as the psychoanalytic therapy, together with a new contribution to the knowledge of man.

III. The Contributions of Psychoanalysis, Neurology, and Endocrinology

I am not concerned here with the details of the psychoanalytic theory or with the technique of psychoanalytic therapy. There exists a vast scientific and popular literature of this field both defending and attacking this new approach to the problem of life and disease. How much of the original concepts will survive, be modified or abandoned, must be left for the future. Psychoanalysis as a theory of personality reaches beyond the realm of medicine into all fields which are concerned with human behavior—the field of anthropology, social sciences, and the problem of education. As a therapy of nervous disorders, it has its definite limitations as all forms of therapy do. Its influence on medical thought in general however can be well defined already.

Historically viewed, the development of psychoanalysis can be considered as one of the first signs of a reaction against the onesided analytical development of medicine in the second half of the 19th century, against the specialised interest in detailed mechanisms, against the neglect of the fundamental biological fact that the organism is one unit and the function of its parts can only be understood from the point of view of the whole system. The laboratory approach to the living organism disclosed an incredible collection of more or less disconnected details, and this inevitably led to a loss of perspective. The fact that the organism is a most ingenious mechanism in which every part cooperates for definite purposes was not only neglected

but defamed as an unsound teleological point of view. It was claimed that the organism develops through certain natural causes but not for a certain purpose. A man-made machine, of course, can be understood on a teleological basis; the human mind creates it for a certain definite purpose. But man was not created by a supreme intelligence —this was just the mythological concept from which modern biology fled, insisting that the animal body should not be understood on a teleological but on a causal and mechanistic basis. As soon, however, as medicine, *nolens volens*, turned toward the problem of the diseased mind, this particularistic attitude—at least in this field—had to be abandoned. In what we call personality the fact that the organism is an intelligibly coordinated unit comes to such striking expression that it cannot be overlooked. William White (*4*) expressed this fact in simple terms. "The answer to the question, What is the function of the stomach? is digestion which is but a small part of the activity of the total organism and only indirectly, though of course importantly, related to many of its other functions. But if we undertake to answer the question, What is the man doing? we reply in terms of the total organism by saying, for example, that he is walking down the street or running a foot race or going to the theatre or studying medicine or what not . . . If mind is the expression of a total reaction in distinction from a partial reaction, then every living organism must be credited with mental, that is, total types of response . . . What we know as mind in all its present infinite complexity is the culmination of a type of response to the living organism that is historically as old as the bodily types of response with which we are more familiar . . . ". Personality thus can be defined as the expression of the unity of the organism. As a machine can be only understood from its function and purpose, the understanding of the synthetic unit which we call body can be only fully understood from the point of view of the personality, to the aims and purposes of which, in the last analysis, all parts of the body are subjected in an intelligible coordination.

Psychiatry as the study of morbid personality therefore necessarily was to become the gateway for the introduction of the synthetic point of view into medicine. But psychiatry could only accomplish this function after it had discovered the personality as its main topic, and this was the accomplishment of Sigmund Freud. Psychoanalysis consists in the precise detailed study of the development and functions of the personality. Although somewhat paradoxically the expression "psychoanalysis" contains the word "analysis" yet its historical significance consists in its synthetic influence.

Psychoanalysis, however, was not the only scientific movement toward synthesis. The development of scientific methods in all fields during the last century resulted in an eager collection of data. Discovery of new facts became the highest goal, their interpretation and correlation in the form of synthetic concepts was looked upon with suspicion as unsound speculation or philosophy in contrast to science. As a reaction to this excessively analytic orientation—a strong desire for synthesis appeared as a general trend of the last decade.

Thus for example, this new synthetic trend can also be clearly observed in non-medical psychology. Here too the tradition of the 19th century was the analytic approach. After the introduction into psychology of the experimental method by Fechner and Weber psychological laboratories sprung up in which now the human mind was dissected into its parts. There developed a psychology of vision, of hearing, of

the tactile sense, of memory, of volition. But the experimental psychologist never even tried to understand the interrelationships of all these different mental faculties and their integration which we call the human personality. Kohler's, Wertheimer's and Koffka's Gestalt psychology can be regarded as a reaction against this particularistic analytic orientation. Probably the most important accomplishment of these Gestalt psychologists has been the clear formulation of the thesis that the whole is not the sum total of its parts but something different from them and that from the study of the parts alone the whole system never can be understood. Just the opposite is true, the parts can be thoroughly understood only after the meaning of the whole has been discovered.

In medicine, a similar development took place. The advances in the field of neurology paved the way for a more comprehensive understanding of the relationships between the parts of the body. It became more and more evident that in the last analysis all parts of the body directly or indirectly are connected with a central governing system and are under the control of this central organ. Not only the voluntary muscles but all the vegetative organs, via the so-called autonomic or vegetative nervous system, are connected with the highest centers of the nervous system. The unity of the organism is most clearly expressed in the functions of the central nervous system. The central nervous system has both the function of the regulation of the internal vegetative processes of the organism and also the regulation of its external affairs, its relations to the environment. The integration of all the external and internal affairs of the organism is the function of a central government represented by the highest centers of the nervous system which in human beings we call the personality. In fact it became obvious that the physiological study of the highest centers of the central nervous system and the psychological study of personality deal with one and the same thing from different points of view. Whereas physiology approaches the functions of the central nervous system in terms of space and time, psychology approaches it in the terms of those subjective phenomena which we call psychological and they are *the subjective reflections of physiological processes.*

Another stimulus for the synthetic point of view came from the discovery of the ductless glands, a further step toward the understanding of the extremely complicated interrelationships between the different vegetative functions of the organism. The system of the ductless glands can be considered also as a central regulating system similar to that of the nervous system: whereas the governing influence of the central nervous system takes place through the conduction of regulating nervous impulses via the peripheral nerve trunks to the different parts of the body, the chemical control of the ductless glands takes place through the conduction by the blood stream of certain chemical substances.

Recently more and more evidence is emerging that probably the functions of the ductless glands ultimately are also subject to the function of the highest centers of the brain, that is to say, to the psychic life.

These physiological discoveries gave us an insight into the detailed mechanism of the fundamental details of how the mind rules the body. The fact that the mind rules over the body, no matter how much it was neglected by biology and medicine, is the most fundamental fact which we know about the process of life. It is the fact which we observe continuously during all of our life. From the moment when we awaken every morning on, our whole life con-

sists in carrying out voluntary movements aimed at the realisation of certain ideas, wishes, the satisfaction of subjective feelings such as thirst and hunger. Our body, this complicated machine, carries out most complex and refined motor activity, under the influence of such psychological phenomena as ideas and wishes. The most human of all bodily functions, speech, is nothing but the expression of ideas through a refined musical instrument, our vocal apparatus. All our emotions we express by physiological processes, sorrow, by weeping; amusement, by laughter; and shame, by blushing. All emotions are accompanied by physiological changes, fear by heart palpitation; anger by increased heart activity and elevation of blood pressure and a change in carbohydrate metabolism; despair by a deep inspiration and expiration called sighing. All these physiological phenomena are the results of complex muscular interaction under the influence of nervous impulses carried to the expressive muscles of the face and to the diaphragm in laughter, to the lacrimal glands in weeping and to the heart in fear, and to the adrenal glands and to the vascular system in rage. All these nervous impulses arise in certain emotional situations during our life in our interaction with other people. The originating psychological situations can only be understood in terms of psychology, as total responses of the organism to its environment.

IV. The Concept of Psychosomatic Medicine: Conversion Hysteria, Organ Neurosis, and Psychogenic Organic Disturbance

The application of these considerations to certain morbid processes of the body led gradually to a new chapter of medicine, to "Psychosomatic Medicine". This expression maybe is not most fortunate because it may imply a dichotomy between psyche and body (soma). If however we understand psychic phenomena as nothing but the subjective aspect of certain bodily (brain) processes this dichotomy disappears.

These psychosomatic studies in combination with psychoanalytic investigations meant an entirely new approach to the study of the causes of diseases. As has been already mentioned, the fact that acute emotions have an influence on body functions belongs to the most common everyday experience. To every emotional situation there corresponds a specific syndrome of physical changes, psychosomatic responses, such as laughter, weeping, blushing, changes in the heart rate, respiration, etc. Because however these psychomotor processes belong to our normal life and have no ill effects, medicine paid until recently little attention to their finer investigation. These changes in the body as reactions to acute emotions are of a passing nature. After the emotion disappears the corresponding physiological processes, weeping or laughing or heart palpitation, or elevation of blood pressure, also disappear and the body again returns to its equilibrium.

The psychoanalytic study of neurotic patients revealed however that under the influence of permanent emotional disturbances, chronic disturbances of the body may develop. At first such chronic bodily changes under the influence of emotion were observed in hysterical patients. Freud introduced the concept of "*conversion hysteria*" in which bodily symptoms develop from chronic emotional conflicts. These changes were first observed in the muscles controlled by the will and in the field of sense perceptions. One of the most important discoveries of Freud was that whenever emotion cannot be expressed and relieved through normal channels through voluntary activity they may become the source of

chronic psychic or physical disorders. Whenever emotions on account of psychic conflicts become repressed, that is to say, become excluded from consciousness and thus from normal expression, they sustain a chronic tension which is the cause of the hysterical symptoms of the body.

Also emotionally conditioned disturbances of the internal vegetative organs which are not controlled by conscious voluntary impulses, such as the stomach or the heart, have been observed. Such observations came not from psychiatrists but from specialists in the field of internal diseases, and led to the concept of "*organ neurosis*". These are disturbances of the internal vegetative organs caused by nerve impulses, the ultimate origin of which are emotional processes most probably localised in the cortical and subcortical centers of the brain. At first the neurotic or functional disturbances of the stomach, the bowels, and of the cardiovascular system became well known under the name of gastric, intestinal, or cardiac neuroses. Another term often used for this type of disorders is "*functional disturbance*", referring to the fact that in such cases, even the finest study of the tissues does not reveal any morphological changes discernible by the microscope. In such cases the anatomical structure of the organ is not changed, only the coordination and the intensity of the organ-functions is disturbed. Such disturbances are considered as less serious because they are reversible, in contrast to those diseases in which the tissues show definite pathological alterations often constituting irreversible damages. Since these functional disturbances are caused by emotional factors, psychotherapy thus gained a legitimate entrance into medicine proper and could not be restricted any longer exclusively to the field of psychiatry. The chronic emotional conflicts of the patient, the cause of the trouble, had to be eliminated by psychological treatment. Since these emotional conflicts arose during the life of the patient in his relationship with other human beings, the patient as a personality became an object of therapy. This is the avenue in which the emotional influence of the doctor upon the patient, medical art, gained entrance into scientific medicine and could not any longer be considered an appendage of therapy, so to speak a last artistic touch in the therapeutic activity of the physician, which in its essence was considered an entirely different, thoroughly scientific procedure. In these cases of organ neuroses the emotional influence of the physician upon the patient became the main therapeutic factor.

The significance of the psychotherapeutic function of the physician however at this phase of development remained restricted to these functional cases considered generally as milder disturbances in contrast to the more serious genuine organic disorders based on permanent tissue changes. Of course in such organic cases the emotional state of the patient had for a long time been recognised as an important issue, yet a real causal connection between psychic factors and genuine organic disturbances had not been generally recognised. Gradually however it became more and more evident that nature does not know such strict distinctions as "functional" versus "organic". More and more clinicians began to suspect that functional disorders of long duration gradually may lead to serious genuine organic disorders based on visible anatomical changes. A few instances of this kind of disorders have been known for a long time, for example that the hyperactivity of the heart may lead to hypertrophy of the heart muscles or that the hysterical paralysis of a limb may lead, due to inactivity, to certain degenerative changes

in the muscles. One had to reckon therefore with the possibility that a functional disturbance of long duration of any organ may lead finally to definite anatomical changes and to the clinical picture of severe organic illness. Intensive psychological and somatic studies of cases of peptic ulcers brought weighty evidence for the assumption that emotional conflicts of long duration may lead as a first step to a stomach neurosis which in time may result in an ulcer. There are also indications that emotional conflicts of another kind may cause continued fluctuations of the blood pressure which constitutes an overtaxation of the vascular system. This functional phase of fluctuating blood pressure in time may cause organic vascular changes and as an effect of these changes a continued irreversible malignant form of hypertension.

These observations have been crystallized in the concept of "psychogenic organic disorder". These disorders, according to this view develop in two phases. The first phase consists of a functional disturbance of a vegetative organ, caused by a chronic emotional disturbance called psychoneurosis. In the second phase the chronic functional disturbance leads in time gradually to irreversible tissue changes, to an organic disease.

V. Progress in Etiological Thought

This view of the causation of certain organic disorders means a remarkable change of traditional concepts. The traditional etiological view, as has been described before, was a localistic one essentially based on Virchow's cellular pathology. The symptoms of the disease are explained by morphological changes in the organs. As to the origin of these morphological changes, different factors have been generally accepted. For a long period after Pasteur's and Koch's discovery of pathogenic micro-organisms the infectious origin of the pathological tissue changes was in the center of research. It was found that the specific diseases are caused by specific micro-organisms according to the point of their attack in the different parts of the body. In these cases the causal chain is: entrance of a specific micro-organism in the body, the dissemination of these organisms within the body through the blood and lymph circulation and further development of the micro-organism in different parts of the body, destroying the normal structure and hence the normal functioning of the cells. This etiological theory could be validated through the experimental introduction of micro-organisms into animals reproducing tissue changes similar to those observed in human beings. This one well-defined mechanism became soon the model for all etiological research.

Apart from micro-organisms other external factors have been discovered as responsible for certain tissue changes —factors such as mechanical, thermic, or chemical influences, the action of which however followed similar principles. For example, the inhalation of certain small dust particles by industrial workers and miners became another well established etiological process. Another generally accepted pathogenic factor is the natural aging process of the organism, explaining such widespread disturbances as the sclerosis of the arteries in later life.

In all these cases the symptoms of the disease are explained as the result of pathological tissue changes which can be traced back to certain external mechanical, chemical or infectious factors, or to the natural aging process. The significance of the new concepts of psychogenic organic disorders consists in the demonstration of a fundamentally different causation of disease.

In these cases the pathological anatomical changes are the secondary results of disturbed function and the disturbed function itself is the result of chronic emotional conflicts. If formerly every pathological function was explained as the result of pathological structure now another causal sequence has been clearly recognized: pathological function as the cause of pathological structure. Although this etiological view is not entirely novel—yet if so explicitly formulated, many clinicians who are raised in the tradition of Virchow's principle and are still under the impressive influence of the simple and experimentally validated etiological discoveries of bacteriology, are not inclined to accept it without reservations. Usually whenever a functional disorder is described it is accepted with some doubt and the hope is expressed that further more precise histological studies will finally disclose tissue changes. The modern clinician is inclined to fall back upon the well proven classical concept that disturbed function is the result of a changed morphological substratum.

So, for example, von Bergman (*1*) who in 1913 still claimed that peptic ulcers are probably the results of a chronic gastric neurosis caused by emotional factors fourteen years later felt the necessity to revise his views, return to a more conservative attitude and to recommend great reservation toward the diagnosis of an "organ neurosis" (*2*). He expressed his belief that in most such cases further research will disclose organic causes. Only slowly can this new concept overcome the traditional views, although it is not in the least contradictory to them. It only shows a different causal sequence in the development of certain diseases, changed function leading to tissue changes in contrast to the opposite sequence, when disturbed function is the result of structural changes.

Previously the scientific *credo* in medicine was that further finer histological studies will reveal an anatomical basis of all so-called functional disturbances; today we feel without questioning the soundness of this principle that in many cases a thorough investigation of a life history might reveal the functional beginnings of truly organic disturbances. In these early phases the disturbance of function has not produced as yet necessarily histologically discernible organic changes. The resistance against this concept is based on the erroneous dogma that disturbed function is always the result of disturbed structure and on the disregard of the opposite causal sequence.

At present it is difficult to foresee what types of organic diseases follow this etiological scheme. It is most probable that in the great chapter of medicine which might be called "Disorders of Unknown Origin", many will fall under this category. Some types of peptic ulcers and of essential hypertension probably belong to this group. Since the functions of the ductless glands are partially under psychic control, for example the adrenal system is influenced by rage, it is probable that many endocrine disturbances in the last analysis will turn out to be the results of chronic emotional disturbances. This is clearly indicated in cases of toxic goitre, the beginning of which often can be traced back to emotional traumata. Furthermore the influence of emotions on carbohydrate metabolism makes it possible that in the development of diabetes emotional factors may play an important causative role.

Essentially this functional theory of organic disorders is nothing but the recognition, apart from *external* causative factors, of *internal* causes of diseases. In other words, many chronic disturbances are not caused by external, mechanical, chemical factors or by micro-organisms, but by the con-

tinuous functional stress arising during the everyday life of the organism in its struggle for existence. All those emotional conflicts which psychoanalysis has recognised at the basis of psychoneuroses and recently also as the ultimate cause of certain functional and organic disorders, arise during our daily life in the social contact with the environment. Continuous fears, aggressions, wishes, if repressed, result in permanent chronic emotional tensions, which disturb the functions of the vegetative organs. Many emotions due to the complications of our social life, cannot be freely expressed and relieved, through voluntary activities, but remain repressed and then are diverted into wrong channels: Instead of being expressed in voluntary innervations they influence the internal vegetative functions, such as digestion, respiration or circulation. As countries thwarted in their external political ambitions often show as a result internal social upheavals, also the human organism if its normal relation to the external environment is disturbed, shows a disturbance of its internal politics, of its vegetative functions.

There is much evidence to show that just as the pathological micro-organisms are specific and have a specific affinity to certain organs so also the emotional conflicts are different from each other and are liable in accordance with these differences to afflict different internal organs. Inhibited rage seems to have a specific relationship to the cardiovascular system, dependent help-seeking tendencies as recent psychoanalytic studies show, seem to have a specific relationship to the functions of nutrition. Again a different and specific conflict between sexual wishes and dependent tendencies seem to have a specific influence upon respiratory disturbances. The increasing knowledge of the relations of emotions to normal and disturbed body functions requires that for the modern physician emotional conflicts should become just as real and tangible issues as visible micro-organisms. The main contribution of psychoanalysis to medicine was to add to the optical microscope a psychological microscope, a psychological technique by which the emotional life of the patients can be subjected to a detailed scrutiny.

This psychological approach to the problems of life and disease brings the internal body processes into a synthetic unit with the individual's external relations to his social environment. It gives a scientific basis to such empirical everyday observations as that a patient often shows marvelous recovery if he is removed from his family environment or if he interrupts his everyday occupation, and thus is relieved from those emotional conflicts which arise from family life or professional activity. The detailed knowledge of the relation of emotional life and body processes extends the function of the physician: the physical and mental care of the patient can again be united in one hand. The division of the healing profession between religion and medicine (—the "lay analyst" is the last residue of this division—) has been an artificial division based on insufficient knowledge of the functions of the body and personality in their mutual interrelation.

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HYPOTHALAMIC FUNCTIONS IN PSYCHOSOMATIC INTERRELATIONS

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I. INTRODUCTION

THE HYPOTHALAMUS developed from the basal portion of the diencephalon under the influence of the medial forebrain bundle in a position favorable for its rôle as a central integrator of several important functions. Receiving afferent fibers from the ascending sensory tracts by way of the thalamus and subthalamus, and sending efferent fibers which directly or indirectly affect the activity of the entire autonomic nervous system, the hypothalamus integrates individual activities of viscera, endocrine glands and smooth muscles with reference to the economical needs of the entire organism. Such regulation and integration of the body's internal milieu serves to maintain what Cannon (*12*) terms homeostasis.

The significance of its position in the sphere of the medial forebrain bundle lies in the fact that the hypothalamus has developed in connection with primitive areas of the forebrain which were concerned in the function of olfaction (*50*). The sense organs concerned with smell were the first distance receptors evolved and they influenced the development of the most primitive or olfactory cortex. Receiving its afferent impulses from primitive olfactory cortex and the great sensory systems, the hypothalamus, as the central organ affecting visceral regulation, was early concerned with olfacto-visceral reflex integration. The functional significance of smell for the acquisition of food, avoidance or preparation against inimical agents and the attainment of objects for sexual satisfaction, indicates the importance that olfaction had in satisfying fundamental instincts. In humans smell has become of less importance, in its function as a distance receptor for stimuli which relieve primary instinctual tensions or hungers, but its anatomical mechanism consisting of olfactory tracts and cortex, hypothalamus and autonomic nervous system are still concerned with the expression of the energies of instinctual life which, in their higher forms, we term emotions. Although this fundamental function remains the same, its dependence upon specific sensations and actual stimuli has been superseded in gradual evolutionary development until, in man, even symbols suffice as stimuli for the gratification and release of instinctual tensions.

The hypothalamus is connected with the cortex indirectly through the thalamus and also by direct afferent and efferent fibers, with the peripheral autonomic system and its lower centers, and with the hypophysis. Thus, it is concerned with several complicated functions all of which are based on its primary capacity of maintaining the

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stability of the organism's internal milieu as the effector agent of the instincts. Related directly to the hypophysis and indirectly to other glands of internal secretion, the hypothalamus 1) regulates endocrine functions and their interrelations; 2) regulates and integrates conservating autonomic functions; 3) is concerned with teleologically defensive and protective reactions which we term emotional expressions and 4) influences the activity of the cerebral cortex in regulation of degree of wakefulness and excitation. Each of these functions will be considered individually with special consideration to its normal and pathological performance in the human.

II. Anatomical Considerations

The hypothalamus is an extremely small structure weighing, as Le Gros Clark (*55*) points out, only 4 grams in an average human brain of 1200 grams. At the base of the brain it is visible only as a small diamond shaped bulge perforated in the center by the hypophyseal stalk and surrounded by the cerebral peduncles and optic tracts. The hypothalamus lies between the mid- and forebrains in the 'tween brain or diencephalon. It constitutes the floor of the third ventricle and extends from the lamina terminalis and anterior commissure cephalad, where it merges with the pre-optic nuclei of the telencephalon, to the tegmentum of the midbrain, caudad, with which it also merges (*52*). It is separated from the thalamus above by the sulcus hypothalamicus and merges laterally with the somatic motor elements of the diencephalic subthalamic nuclei.

Interest in the human hypothalamus decreases our concern with lower forms; in fact, to homologize the various hypothalamic nuclei is difficult due to the positional changes accompanying foreshortening and deepening of the third ventricle to conform to the large growth of the primate telencephalon. The hypothalamus is relatively smaller than in lower animals except for the pars mammillaris which has increased in size. Added to these difficulties in homologizing are the reports of zealous subdividers who demarcate identical nuclei as new nuclear masses and apply new names to them. In the dog, from 12 to 21 discrete hypothalamic nuclei have been reported by various investigators.

Throughout the animal series hypothalamic nuclei, with the exception of a single posterior group of cells, are composed of small oval and fusiform cell bodies with scanty cytoplasm, vesicular nuclei and several short processes, all characteristic of central structures belonging to the autonomic nervous system (*4*). Their position close to and beneath the sulcus hypothalamicus is homologous to the position of spinal vegetative structures within the lateral gray columns.

Grünthal (*35*) described a more complicated cell structure in the human embryonic than in the adult hypothalamus and attempted to relate it with an observable progressive simplification of the cell grouping in evolution; the human hypothalamus has the least complicated structure. Le Gros Clark has shown that the lateral mammillary nucleus is smaller in man but that the lateral hypothalamic area or the large celled nucleus mammillo-infundibularis is more complicated and difficult to analyze. In man the medial mammillary nucleus reaches its largest size and this growth is accompanied by an increased differentiation of the antero-ventral nucleus of the thalamus and the connecting mammillo-thalamic tract.

The anterior hypothalamus is composed of several nuclei. Two *pre-optic*

nuclei, lateral and medial, lie below the anterior commissure. They send fibers posteriorly into the main body of the hypothalamus, thalamic peduncle and thalamus. The *paraventricular* or *filiform nucleus* lies along the wall of the third ventricle and consists of large multinucleated colloid filled cells which to the uninitiated, give the appearance of being degenerated. Their normal appearance has been described in human cases as evidence of central pathology in diabetes mellitus, psychoses, etc., and their unusual structure has misled investigators searching for experimental retrograde degenerations (*41*). The colloid material has suggested to some that they elaborate hormones or even that they have engulfed colloid which ascends the infundibulum from the pars media of the hypophysis. The paraventricular cells give rise to fibers which terminate in the thalamus, tuber cinereum and preoptic nuclei, and descend as low as into the medulla oblongata, although controversy exists as to their ultimate destination. It has been thought by some that the fibers descend as low as the thoracic cord (*9*) and by others that they exit by way of the vagus nerve. However, it is probable from recent experiments that the descending hypothalamic fibers do not form a compact bundle but descend by short chains of crossed and uncrossed intercalated neurones. (*41*). The *supraoptic nucleus* lies above and straddles the optic chiasm. It also consists of large bipolar cells filled with colloid and like the paraventricular nucleus has a rich vascular bed. Its fibers descend the stalk of the hypophysis to the posterior lobe as the supra-optico-hypophyseal tract.

The middle hypothalamus or *pars tuberalis* contains the *ventromedian* and *dorsomedian* nuclei which are only relatively circumscribed portions of the diffuse small autonomic cells of the substantia grisea centralis. The *lateral hypothalamic* or mammillo-infundibular nucleus is extremely complicated in man and extends throughout the middle and posterior hypothalamus imbedded in the medial forebrain bundle. Its cells are larger than those of the median nuclei.

In the posterior portion of the hypothalamus is a large *posterior hypothalamic* nucleus lying above and in front of the mammillary bodies and composed of large motor cells. Its fibers descend through short neuronal chains to the lateral grey columns at various spinal levels and form a chief efferent system from the hypothalamus. The pars mammillaris is composed of a large *lateral mammillary* nucleus, small *medial mammillary* nucleus and two small aberrant premammillary and supramammillary nuclei.

The *fiber systems* and connections of the hypothalamus are known only grossly (*30*). The fornix connects the hippocampus, which reaches its highest development in man, to the mammillary body and this in turn communicates with the anterior nucleus of the thalamus by way of the mammillothalamic tract or bundle of Vicq d'Azyr. Thalamic fibers from the anterior nucleus reach the cortex of the cingulum. Thus, there is a direct and indirect system of communication between the posterior hypothalamus and the olfactory cortex, which attains its most complicated development in man. Descending fiber-bundles arise from the mammillary body and from the entire hypothalamus, are collected in a periventricular bundle and distributed to the thalamus and brain-stem by way of the dorsal longitudinal bundle of Schütz. Fiber connections exist between hypothalamus and thalamus, subthalamus and globus pallidus. Frontal lobe relations are effected indirectly through the medial thalamus,

and a direct fiber pathway has also been described.

The significance of these anatomic connections of the hypothalamus has recently been stressed by Papez (*68*). He calls attention to the fact that the hypothalamus receives an incoming stream of sensory impulses not only from the thalamus but from the subthalamus also. Optic impulses enter from the nucleus pregeniculatus of the lateral geniculate body, auditory from the ventral part of the medial geniculate body, pain from the reticular nucleus of the spinothalamic and trigeminothalamic systems and touch from medial lemiscus fibers ending in the mamillary peduncle. Thus, the hypothalamus receives afferent impressions through all somatic and visceral sensory modalities. Its efferent systems to the hypophysis from the pars optica and to lower autonomic centers from the pars tuberalis have been described. Afferant connections from the cortex arise from the hippocampal system by way of the fornix so that hypothalamic activity may be stimulated or inhibited by the cortex. Efferent fibers from the hypothalamus arise, especially from the mammillary body, by way of the bundle of Vicq d'Azyr to the anterior thalamic nucleus from which radiations proceed to the gyrus cinguli. From this cortical structure hypothalamic impulses may radiate to other parts of the cortex. Thus, the hypothalamus lies as a central organ, intermediate between the cortex and the peripheral autonomic system, connected directly and indirectly with both territories by a two-way neural system of fiber pathways.

The *blood supply* of the hypothalamus has been studied carefully because of its functional implications. The circle of Willis surrounds the hypothalamus and supplies numerous small branches which have a discrete area of distribution in zones, so that isolated thromboses may cause discrete lesions and result in a circumscribed symptomatology. Popa and Fielding (*67*) believe a portal circulation from the pituitary body brings secretory products to the hypothalamic nuclei where their effects are exerted upon the autonomic cells. Wislocki and King (*80*), however, were unable to confirm this anatomical observation.

III. Endocrine Functions

An outpouching of the floor of the third ventricle gives rise to the posterior lobe or neurohypophysis which is a derivative of the primitive hypothalamus. In the adult the posterior lobe of the hypophysis is connected to the hypothalamus by the infundibulum through which passes the supra-optico-hypophyseal nerve tract which conveys descending fibers from the supra-optic and paraventricular nuclei. Other evidence, to be discussed later, indicates that these nuclei subserve parasympathetic functions so that according to Fulton (*24*) this fiber tract should be considered as an outflow of the cranial parasympathetic division of the autonomic system. A few descending fibers enter the pars media from the suprachiasmic nucleus. The anterior lobe has no direct hypothalamic innervation but receives orthosympathetic fibers from the superior cervical ganglia by way of the perivascular network along the intracranial blood vessels and is thereby indirectly under the influence of the hypothalamus.

The close proximity of hypothalamus and pituitary body has created great difficulty in determining the source of a particular symptom in clinical syndromes arising from lesions in this area (*70*). Functional investigations in man are so difficult that at one time the hypophyseal-hypothalamic syndromes

were dismissed as arising from disturbances of both structures considered as a physiological unit. Adiposity and emaciation, genital dystrophy and pubertas praecox are even now disturbances observed in humans for which the basic lesion is not clearly either hypophyseal or hypothalamic and until clear-cut animal experiments gave unequivocal results, diabetes insipidus was also imperfectly understood. The reason for these uncertainties lies in the fact that the pathological bases for syndromes originating in this region are most frequently pituitary tumors, craniopharyngiomas or cysts which implicate both structures by pressure. Trauma associated with basal skull fractures, basal meningitis, are likewise unlocalized in their effects. However, vascular thromboses, lethargic encephalitis, chronic alcoholism and multiple sclerosis involving the hypothalamus do not implicate the hypophysis, and in these conditions disturbances in fat and carbohydrate metabolism and in genital development are frequently observed, indicating a primary hypothalamic implication.

The hypophysis has been recognized as the master gland of the endocrine system, functioning as the elaborator of many hormones most of which influence the action of other glands. It functions from its cephalic position as an integrator of general grandular activity very much as the hypothalamus regulates autonomic nervous structures. The close association of the two structures, their common embryonic derivation (at least part of the pituitary), and the nervous innervation of the gland from the hypothalamus further indicate the possibilities of a close functional cooperation.

According to modern endocrinologists, the endocrines fulfill a three-fold function of communication, correlation and catalysis which contribute to the mechanisms concerned in the preservation of an adequate internal milieu of the body, but are relatively slow acting and chronic in effect. Hypothalamic structures through their neural connections with the autonomic nervous system, innervating all smooth muscles and glands, regulate and integrate the internal milieu with greater speed and less lasting but more violent effect. It has been found that denervation of most endocrine glands, which also means removal of the central influences from the hypothalamus, produces no profound insufficiency. This signifies that although the rapid, often emergency effect of their activities is lost, their constant activities are preserved as long as the pituitary is intact. Parasympathetic posterior lobe and probably adrenal cortex functions are, however, dependent on an intact nerve supply.

Cushing (*14*) has long maintained that secretory products of the intermediate lobe of the pituitary, consisting of colloidal material, obtain entrance into the general systemic circulation through the third ventricle. Lately he has considered that the hormone exerts its effect directly on the cells of the hypothalamus. The colloidal bearing cells of the supra-optic and paraventricular nuclei suggest to some that these cells pick up the hypothetical ambulatory secretion of the hypophysis. Others maintain these cells are in themselves secretory. No decisive evidence is available at present.

Diabetes insipidus is a clinical entity characterized by an excessive thirst and polyuria, often accompanied by emaciation. Damaging lesions of the posterior lobe of the hypophysis such as are caused by neoplasms result in this syndrome (*20*). Extracts of posterior lobe compensate for the deficiency of a posterior lobe hormone. However, diffuse lesions of the hypothalamus in

multiple sclerosis or encephalitis often produce the same syndrome. Extensive experimental work has shown that the supra-optic nucleus, its tract and the posterior lobe constitute a neuroglandular unit which affects production of an antidiuretic hormone controlling the function of diuresis residing in the anterior lobe as part of its general control over metabolism. Lesions anywhere in the system permit uncompensated anterior lobe function to become excessive and result in polydypsia and polyuria. It is thus not surprising that many pathological processes involving either pituitary or hypothalamus give rise to diabetes insipidus as a symptom. It has been confused with psychogenic polydypsia, sometimes seen in the purification ritual of schizophrenics but the organically derived thrist is relieved by pitressin.

From the posterior lobe, extracts can be prepared which have a pressor and oxytocic effect. It is not clear that these represent hormones rather than pharmacological substances. There is some evidence that retinal fibers entering the supra-chiasmic nucleus, relayed to the pars media, are concerned in the production of skin pigmentation.

Other functions of the hypothalamus concerned with internal secretions are far less clear and have not been definitely separated from anterior lobe functions. The paraventricular nucleus has been implicated in the cause of *diabetes mellitus* and, according to Morgan, (*62*) atrophies in the disease in man. However, the lesions of the lateral portion of the tuber cinereum like hypophysectomy prevent pancreatectomized dogs from diabetes. Posterior hypothalamic stimulation assists in the mobilization of carbohydrate reserve through excitation of the adrenals, and damage of the paraventricular nucleus increases sensitivity to insulin. Others consider the ventromedian tuber nucleus to be concerned in control of liver, prancreas and adrenal cortex. This has all yet to be confirmed and only indicates that the posterior hypothalamus may be concerned in the function of these glands not only in their rapid excitation in response to emergencies but perhaps also in their constant level of activity. Basal skull fractures with injury to the base of the brain are often followed by temporary glycosuria. Operations in this region are associated with a transient glycosuria and parasellar neoplasms also cause deviations in carbohydrate metabolism. However, none of these clinical disturbances are of localizing value.

Adipositogenital dystrophy is a clinical syndrome frequently associated with parasellar tumors that involve both hypophysis and the tuber portion of the hypothalamus. Retardation of sexual development in the young and loss of function in the adult are not uncommonly associated with deposition of fat. It is not clear which portion of this syndrome comes from the gland or the neural tissue, or even that either is necessarily hypophyseal in origin. There is suggestive evidence that adiposity, uninfluenced by hormone administration, arises from lesions of the hypothalamic region and genital dystrophy as a disturbance of the pituitary influence on growth and of its specific gonadotropic hormone. In the rabbit ovulation can be stimulated by hypothalamic stimulation, according to Harris (*37*). In the human, purely hypothalamic lesions have been associated with genital dystrophy in the male and amenorrhoea in the female, not influenced by administration of pituitary or gonadal extracts. On the other hand, pubertas praecox, induced by tumors of the pineal body has been observed in hypothalamic lesions, so that this

supposedly pathognomonic sign of pineal tumors may be the result of pressure forward, on the hypothalamus Similarly, adiposity without hypophyseal lesions and unresponsive to the administration of anterior lobe extracts is known clinically. Hypophyseal cachexia or Simmond's disease originally ascribed to atrophy of the hypophysis has been observed in tumors involving only the hypothalamus, the hypophysis being normal. Non-neoplastic hypothalamic lesions may cause the same disturbance of fat metabolism.

It is now certain that diabetes insipidus or abnormal water metabolism may be related to a disturbance of the hypothalamus. Furthermore, diabetes mellitus, involving an abnormality in carbohydrate metabolism, obesity or emaciation as evidence of disordered fat metabolism and disturbances in ovulation, menstruation and sexual maturation may be due in part or whole to lesions of the hypothalamus. Whether they are due to loss of a direct and specific control, or an indirect influence, of the hypothalamus on the hypophysis, pancreas, adrenal cortex or gonads is not yet known.

IV. Central Regulative Functions

Since Claude Bernard indicated the importance of the maintenance of a stabilized internal milieu of an organism for its normal existence, the importance of the autonomic nervous system in that function has been recognized (*12*). Although the sensory and motor systems are concerned with relations of the individual to its external environment, they operate under the influence of the autonomic nervous system serving to free the internal conditions of living from tensions created by external events, and to attain those stimuli which enable internal tensions to be discharged. It is too often implied that autonomic functions are only concerned in adjustments to external happenings by increasing or decreasing internal activities or by emergency massive integrated discharges. They are also effective in directing the external discharge of tensions which are basically internal and instinctual, the energy of which we term emotion.

Between the somatic and autonomic nervous systems there is an interdependence and reciprocal action so well described by Hess (*40*). This intimate cooperation occurs at all levels of the nervous system for both divisions are ubiquitously represented, often approximated so closely that anatomic separation is difficult. The more highly developed the organism and the more complicated and evolved its somatic functions, the more the autonomic components of adjustment have attained encephalization and control. Thus in the higher animals the hypothalamus attains more the rôle of a superior central regulating organ of visceral function subordinating brain-stem, medullary, spinal and peripheral centers. It attains this complicated function in conjunction with an equally complicated and developed thalamus and thalamo-cortical relationship that accompanies behavior which is less automatic and reflex, but more purposeful.

Not only does the hypothalamus integrate all of visceral and autonomic activity but it functions as a balancing mechanism between parasympathetic and orthosympathetic divisions. The parasympathetic system is associated with anabolism, lessening the efficiency of the sensorimotor system and operating in the interest of individual organs. It furnishes the brake upon activities, conserves resourceses and reserves and builds up tensions. The orthosympathetic system lies exterior to the visceral organs and enhances the functions of

the sensorimotor apparatus, increasing its functional output. It is concerned with catabolic activity in massively discharging internal tensions. The fine cooperation of these two divisions results in the balancing of effects and maintenance of an integrated regulated internal milieu, within certain limits of stress. This is done by no strict antagonism in function, for specifically opposite effects of the two divisions have been demonstrated only in respect to their influence on bladder, gastro-intestinal, arteriolar and sudomotor tone. A more general inhibitory control, however, is manifested by the anterior parasympathetic centers upon posterior orthosympathetic mass activity.

Since the discovery of the hypothalamus as a visceral center a multitude of separate functions have been ascribed to it. Excitation of this structure effects rise in blood pressure, arteriolar contraction, dilatation of the pupils, elevation of the hairs, increase in blood sugar and circulating adrenaline, dilatation of the bronchioles, increase in heart rate, contraction of bladder, uterus and gastro-intestinal tract (*65*), secretion of tears and saliva, regulation of body temperature and sleep regulation. All these are in addition to the metabolic functions concerned in water, carbohydrate and protein metabolism and control of growth and sexuality (*44*).

As Beattie (*55*) points out, so many functions associated with an anatomical structure of such small size makes it improbable that there are multiple discrete centers except those controlling antidiuretic, diabetogenic and pigmentary hormones of the hypophysis. Rather, the hypothalamus as a unit contributes to widespread activities which can be categorized into a few groups. As a matter of fact, those who have carefully stimulated hypothalamic fields of microscopic size with the Horsley-Clark stereotaxic machine have found each hypothalamic function represented over a rather wide extent of structure.

If the hypothalamus is an autonomic center concerned with maintaining a constant internal environment, it probably has two general systems each with their own afferent and efferent connections and acting reciprocally to each other. There is considerable evidence that these dual centers exist. The posterior hypothalamus is an orthosympathetic and the anterior a parasympathetic center (*18*).

Change in temperature has been used by Beattie (*55*) to exemplify the integrating role of the dual hypothalamic centers. Exposure to cold is associated with attempts at conservation of body heat and increased heat production. There results a peripheral vasoconstriction, rise in blood pressure, increased heart rate, apneustic respiration and increased oxidation of carbohydrates. To increase heat production shivering finally ensues. Stimulation of the posterior hypothalamus evokes contraction of peripheral arterioles, increase in blood pressure and blood sugar, and apneustic respiration (*56*). Urine secretion is increased and the bladder and stomach walls relax. Destruction of the posterior hypothalamus causes a fall in body temperature and absence of shivering response. Thus, conservation of body heat is an orthosympathetic posterior hypothalamic function, accomplished through an integration of a widespread activity of the autonomic system, influencing the functions of many organs in the direction of increased activity.

Increase in external heat results in measures to increase the loss of internal heat. The peripheral vessels dilate, warm sweat secretion is increased, the blood pressure falls and the heart slows. This same activity results from stimu-

lation of the anterior hypothalamus in the region of the septal and pre-optic areas. This area is probably parasympathetic in function. Experiments have shown that stimulation can also effect contraction of the bladder wall (*49*) and fall in blood pressure.

Experimental lesions of the anterior hypothalamus result in hyperthermia and of the posterior hypothalamus, in hypothermia (*72*). Alpers published several cases in humans in which this localization was confirmed by anatomical studies. Tumors of the hypothalamus produce marked disturbances of temperature regulation. Hypothalamic inflammatory lesions, traumatic lesions of the base of the brain and other human diseases confirm the presence of heat regulating centers (*18*). The most convincing evidence for localization of the dual thermostatic mechanism in man comes from surgical operations. Operations on the parasellar region, especially for exploration of gliomas of the optic chiasm, frequently result in a fatal hyperpyrexia accompanied by flushed dry skin and panting respiration. Operations through a suboccipital decompression, during which the brainstem is manipulated, disturb the posterior hypothalamus and result often in hypersomnolence, subnormal temperature and cold, cyanotic body surfaces.

Cushing (*14*) showed that most patients with craniopharyngiomas and compression of the pituitary stalk have an unaccountably low blood pressure. He injected pituitary substance and pilocarpine into the lateral ventricles of patients and observed marked flushing of the entire skin, excessive sweating, fall in rectal temperature, blood pressure and basal metabolic rate, and increase in gastro-intestinal activity, all evidence of excitation of parasympathetic structures which we now know to be located anteriorally in the hypothalamus. The entire attack could be abolished by atropine. Cushing's results of parasympathetic excitation on gastric function, i.e., increased peristalsis, pylorospasm, hypersecretion, retching and vomiting, he considers to be the basis of gastric erosions and ulcers found at postmortem examination in patients with tumors of the third ventricle.

Epileptic attacks of a specific type arising from irritation of the posterior hypothalamus have been recognized since the publication of an oft-quoted case of Penfield (*69*). His patient had a ball-valve tumor of the third ventricle which periodically gave rise to severe seizures. They were initiated by a sensation of fever during which the body surfaces became flushed, respiration slow and perspiration copious. Saliva and tears flowed profusely; the pupils enlarged and exophthalmos appeared. Hiccoughing and shivering were violent; the pulse varied in strength and rapidity. Penfield attributed these disturbances to excitation of the thalamus, wherein he postulated that the superior autonomic centers lay, but animal experimentation clearly indicates that the disturbance can be correlated with irritative lesions of the posterior, lateral hypothalamus. The syndrome is predominately an *orthosympathetic epilepsy*. Morgan (*62, 63*) produced similar epileptic attacks in animals, abolished by denervating the adrenals, thyroid and parathyroid glands through which he concluded the peripheral effect was mediated. Furthermore, in a few cases of epilepsy in humans he described degenerative changes in the hypothalamic tuber nuclei, which were, however, not convincing. *Parasympathetic epilepsy* has been observed in its pure form only in the experiments of Cushing described above.

Human disorders of the hypothal-

amus give little in the way of localizing value to a particular symptom in the epileptic syndromes due to irritation. Tumors of this region cause a variety of attacks accompanied by syncope, cyanosis, flushing, slowed or increased respiration, lowered or raised blood pressure and temperature, etc. In these attacks fragments of para- and ortho-sympathetic responses are mixed as would be expected from a large pressing mass. Occasionally in epidemic encephalitis fragmentary manifestations may occur involving but one function. Panting dyspnoeic attacks are not uncommon, nor are attacks of localized flushing and perspiration in the chronic encephalitics.

Ranson (*71*) and his co-workers, using the Horsley-Clark apparatus, stimulated the lateral portion of the posterior hypothalamus and caused struggling, biting and clawing with dilatation of pupils, increased respiration, elevation of hair, salivation and sweating, along with inhibition of gastro-intestinal activity. These evidences of massive sympathetic discharge are identical to those observed in normal animals in fright. They constitute an expression of intense emotion. In the experimental animals an increase in adrenin and sympathin was demonstrable in the blood stream (*57*).

Such massive discharges are seen only rarely in humans and then not in their entirety. Certain cases of tumors of the third ventricle give rise to some of these manifestations accompanied by a feeling of apprehension. In chronic encephalitis one occasionally observes spontaneous manifestations of rage without appropriate external cause, in which the patient feels angry and shows the corresponding signs of massive discharge of the orthosympathetic system. From experimental and clinical evidence there seems to be little doubt that the integration of the economically vital peripheral processes in emotional expressions of rage or fear occurs centrally in the hypothalamus.

Concerning the physiology of sleep much has been conjectured in relation to its central mediator. During the first epidemic of lethargic encephalitis in 1890, known as Nona, Mauthner (*58*) correlated the pathological sleep with lesions in the floor of the third ventricle. The subsequent epidemic of this century has served to confirm the clinical impression that the hypothalamus has much to do with the function of sleep.

According to Hess (*40*) sleep is a positive adjustment as a protection against exhaustion. It indicates a rejection of stimuli and inhibition of sensorimotor functions through autonomic influences. Kuppers (*53*) considered that a connecting link between cortex and peripheral nervous system disengaged in sleep and resumed connections on awakening. The cortex seems to be dominated by a regulative action of the autonomic system in the form of a protective reflex. It is obvious that the phenomenon of sleep is not the sole evidence of autonomic influence, for changes in blood pressure, heart rate, distribution of circulation, respiration, temperature and smooth muscle tonus are universally present in sleep. The change in psychic activity parallels these peripheral alterations. The hypothalamus, in which a balance between parasympathetic and orthosympathetic control over internal activities is found, acts in modifying the functional preparedness of the sensorimotor cortex.

The exact localization of a sleep center has not been possible on clinical evidence (Fulton and Bailey) (*27*). Rowe (*74*) believed, on the basis of human cases, that the lesion which produced hypersomnolence may be in the medial thalamic nucleus or in the thalamico-

perventricular-hypothalamico-mesencephalic chain of neurones.

Demole (*16*) was able to produce sleep by injection of calcium into the floor of the third ventricle. Ranson (*71*) was able to produce somnolence in experimental animals by placing a lesion in the posterior hypothalamus in the region of the mammillary bodies at the transition between hypothalamus and midbrain, blocking the passage of impulses from the hypothalamus to caudad structures. Somnolence could be produced without damaging any sensory pathways to the cerebral cortex. The lesions were in those same areas which when stimulated produced signs of excitement. Ranson's (*45*) animals showed in addition to hypersomnolence, falling asleep when undisturbed, blank mask-like facies and cataleptic attitudes of the extremities. There was loss of motor initiative, disinclination to walk or eat, acceptance of passively induced poses, vacuity of expression and suppression of emotional reactions. Somnolence is associated with fall in body temperature and metabolic rate (*26*). Human encephalitics with disturbances in sleep rhythm show marked lack of evidence of emotional expression, blank masked facies and general akinesia. Studies now in progress by Grinker, Reich and Kobrin indicate that psychologically these people are rather passive, optimistic and hopeful when their reality has been years of slow progression of symptoms. This serenity is only occasionally broken into by a sudden unprovoked rage attack.

There is some doubt whether a sleep center exists in the hypothalamus or in any basal structure. Somnolence results from destruction of the area, stimulation of which causes emotional excitement. Stimulation experiments by Hess may have been accompanied by small electrolytic lesions (*24*). Yet in humans, sleepiness was evoked by stimulation of the exposed posterior hypothalamus at operation (*28*). Although the problem is far from solved, most of the evidence suggests that the hypothalamus functions in an excitatory role, increasing states of activity; that inactivity and sleep is a negative phase which arises through inhibition of the hypothalamus, possibly from the cerebral cortex.

Natural experiments in humans produced by disease processes are of little localizing value for physiological conclusions except in rare, sharply localized tumors or softenings. Therefore, in human cases in which the hypothalamus is involved, knowledge of exact experimentation must be drawn upon, which is methodically valid except when the higher qualities of emotion are considered. Trauma, operative manipulation, tumors, vascular lesions and infections are etiological factors which produce an intricate combination of disturbances of hypothalamic functions. Fulton (*24*) considers that there are five main clinical syndromes in man arising from the hypothalamus: 1) hyperthermia from anterior lesions; 2) diabetes insipidus and emaciation from anterior lesions; 3) adipositogenital dystrophy from lesions of the middle portion; 4) hypersomnia and hypothermia from the posterior portion; 5) epileptic autonomic discharges: parasympathetic from anterior irritation, orthosympathetic from posterior irritation. There are, however, miscellaneous combinations of these, isolated disturbances of sleep and tone as in narcolepsy, respiratory disturbances as in encephalitis as well as disorders of sweat secretion. The great variety of syndromes due to organic lesions of the hypothalamus indicates the possibilities of bizarre and complicated functional or psychogenic disturbances utilizing the same anatomical mechanisms.

V. Cortical Influences on the Hypothalamus

Cannon's (*11*) studies on the homeostatic functions of the autonomic nervous system extended to its participation in emotional reactions or expressions. He concluded that emotion was not a central reverberation of peripheral autonomic changes, as the James-Lange (*54*) theory postulated, but that the visceral manifestations were secondary to a function of a central nucleus which effected purposeful peripheral changes (*11*). His analysis of the economic rôle of the autonomic nervous system in the body's reaction to anger or fear are summarized by Kempf (*51*) as follows:

> Any form of potentially harmful stimulus, whether it stimulates the visual, auditory, olfactory, gustatory, cutaneous, or the entero- or prioprio-receptor fields, tends to cause a more or less vigorous fear or avertive reaction which is promptly followed by a compensatory reaction which either removes the painful stimulus from the receptor (fight) or the receptor from the painful stimulus (flight). In order that this vitally necessary procedure shall be quickly and safely accomplished the autonomic apparatus has developed the capacity to compensate by increasing the amount of glycogen and adrenin in the blood, by increasing coagulability of the blood, by regulating the blood supply so that the organs necessary for the immediate struggle shall be given an increase of blood supply, by appropriately changing the blood pressure, by increasing the rate and amplitude of the heart beat, increasing the dilatation of the bronchioles and the working powers of the muscle cells.

Bard (*7*) was able to show conclusively that this central autonomic center resided in the hypothalamus. Removing the brain above the hypothalamus produced a struggling, lashing, clawing, snarling animal showing signs of massive orthosympathetic discharge. These were dilatation of the pupils, rise in blood pressure, increased heart rate, sweating, elevation of hairs, etc. These reactions constituted a "sham rage" since no consciousness of the emotion was possible. The intensity of the reactions decreased if the animals were not restrained but then they were markedly restless. Removal of the hypothalamus abolished these responses. Furthermore, Ranson (*71*) stimulated the lateral posterior hypothalamus in the intact animal and evoked identical sham rage reactions. Thus there is little doubt that the hypothalamus is the essential central organ for integration of emotional expression.

Bard's experiments (*6*) also clearly indicate that the hypothalamus is normally inhibited by the cerebral cortex. The possible anatomical mechanisms for such inhibitory influences are 1) from the gyrus cinguli through the anterior medial thalamic nuclei to the hypothalamus, 2) from the hippocampus by way of the fornix to the mammillary bodies and 3) from hypothecated direct fronto-hypothalamic tracts.

The hypothalamus is not the only center for autonomic activity nor is it the most cephalad. At each level of the nervous system such centers exist, i.e., spinal, bulbar, pontine, etc. The hypothalamus re-represents visceral activity in more special, highly organized combinations. Its orthosympathetic areas control and integrate all visceral activity, its parasympathetic areas are more highly specialized and discrete.

However, autonomic representation exists in the cerebral cortex both of parasympathetic and orthosympathetic type. Stimulation of the cerebral cortex evokes alterations in the cardiovascular system, body temperature, sweating, pilomotor system, intrinsic ocular muscles, gastro-intestinal system and bladder. These visceral reactions are elicited

from the neighborhood of related somatic motor centers indicating an overlap of cortical autonomic and somatic representation. An overlap in the sensory field has also been postulated. As a result of such overlap, specific movements arising from the cortex are accompanied by simultaneous specific changes in blood supply, sweat secretion, etc., which apparently facilitate and increase the efficiency of the movement desired. These cortical functions are mediated partly through the hypothalamus but also independent of it through extrapyramidal and possibly pyramidal motor fibers.

This overlap is lucidly described by Fulton (*24*) as follows:

> The autonomic division of the nervous system can no longer be regarded as a purely peripheral system, but rather as an elaborately organized division of the central nervous system with representation at all levels. At each level, moreover, the somatic and autonomic systems dovetail with one another and while the somatic may predominate in a given region—and thus obscure the autonomic component—it is generally impossible to evoke a somatic reflex that does not have an autonomic concomitant of central origin. . . . When, therefore, the intact picture is conjured up of two great interlacing systems—which share some receptors in common but which have others that are specific—and which discharge together in a synergenic manner that makes for unification of reaction in the organism as a whole.

Although hypothalamic activity integrates all autonomic functions it includes but few somatic responses. Panting, shivering, running movements and clawing are the extent of somatic responses from direct excitation of the hypothalamus. Cortical autonomic responses are all in association with a corresponding somatic innervation. It seems likely that the hypothalamus in its most vigorous activity utilizes the somatic system to facilitate its release of tensions in the service of instinctual reactions; the cortex utilizes specific autonomic functions in the economy of volitional or "least automatic" movements. In this cooperation of synergism, the close association of somatic and autonomic activity further indicates how their separation is impossible, for as we shall see later, the cortex driven by the autonomic system in turn uses autonomic activities to further cortical responses, yet inhibiting their excessiveness.

The peripheral fine and coordinated movements arising from stimulation of the motor cortex are possible only if the cruder, more massive movements of the older motor system are inhibited, and postural tonus is relaxed. Encephalization of function thus is accompanied by inhibition of lower, more massive reflex responses of the extrapyramidal systems. So, too, finely adaptive visceral changes accompanying cortical responses are possible only by inhibition of cruder hypothalamic massive visceral responses. We can compare the relation of the hypothalamus to cortical autonomic centers as the extrapyramidal motor system to cortical motor areas. Removal of the latter results in overactivity of the previously inhibited extrapyramidal system. Removal of the cortical autonomic centers results in overactivity of hypothalamic functions.

Thus, we see that the cortex damps down hypothalamic responses and permits its activity upon appropriate occasions and then in graded and modulated fashion. Were this not the case stimuli of all sorts would evoke rage and flight reactions incapable of restriction. However, instead of such reflex behavior the normal adult is able to develop a more adaptive response.

Clinical cases showing evidence of release of hypothalamic function from cortical control are rare. Tumors and

infections have been observed, associated with wild, grotesquely violent behavior possibly due to interruption of the cortico-hypothalamic inhibitory fibers. Chronic encephalitis in children often produces rage-like states and in some of the organic psychoses release of hypothalamic mechanisms is suggested. Yet in no case has it been demonstrated that the specific pathway was anatomically interrupted so that our conclusions are all by analogy to animal experiments. Yet the significance or normal cortical inhibition of the hypothalamus in the intact human being is of great importance to our theoretical concepts concerning abnormal emotional expressions.

In the hypothalamus there are neural patterns responsible for emotional expressions and behavior, which are normally inhibited by the cortex, and it is in the cortex that feelings of emotions are evoked. Both activities exist in the normal person in cooperation. The better conditioned a stimulus, the less direct emotional expression it elicits, whereas strange or sudden, unconditioned stimuli produce a more direct and violent reaction.

VI. Hypothalamic Influences on the Central Cortex

Experiments concerned with hypothalamic release from cortical control furthered our knowledge of that structure as an organ for emotional expression. Animal experimentation has also served well to show the function of the hypothalamus in autonomic and endocrine regulation. However, its function in influencing the cortex as expressed in direction of thought and conscious feelings can be determined only in man. With this in mind Grinker (*32*) experimenting on cats was able to show that excitation of the hypothalamus could be produced by electrical shocks passed through the underlying bone in an intact animal. He was also able to show that typical action currents could be obtained from the hypothalamus through the bone, and since cortical action currents had already been well studied with the so-called electroencephalograph through the intact skull, a valuable method was at hand for studying corticohypothalamic relations in man.

The next step consisted in constructing an electrode which was suitable for experiments on man. This and the technique of its use have been reported by Grinker and Serota (*33*) and recently confirmed by Hoagland et al (*41a*). It will be briefly described here since it is hoped that others will use it to answer many important problems which require human experimentation.

The hypothalamic lead for the human consists of a sharply tipped steel drill rod about 3 mm. in diameter and 16 cm. long with a slight upward concavity at its terminal third. It is insulated with celluloid and Duco-cement except at its tip which for 2 mm. is heavily silver-plated. The other end is arranged for the attachment of fine wire to an electroencephalograph or stimulating inductorium. The details of the electrical connections will be dispensed with here as they are typical to any electroencephalographic arrangement.

The human hypothalamus lies above or just behind the sphenoidal air sinus which ends posteriorly at a point about the middle of the floor of the sella turcica. The hypothalamus is closest to the base of the skull just back of the sinus and over the sella. Between it and the bone are dura, subarachnoid space and hypophysis. The nasal mucous membranes of one nostril are cocainized with the patient in a sitting position. The lead is then slowly passed through the nasal passage and on

reaching the posterior pharyngeal wall it is tipped upward to engage the pharyngeal mucosa at the junction of the roof of the vault and the posterior wall. The needle tip is then firmly pushed through the mucous membrane, mucosa and periosteum into the sphenoidal bone. As it engages a crunching sound is heard and the electrode becomes firmly embedded. A momentary pain is felt on insertion but this passes off at once and patients are comfortable and able to speak, swallow and walk about unhampered. Removal of the lead is simply accomplished, by a sudden jerk and no antiseptic is necessary. No infections have been observed. The lead in position may be used for either stimulation, registration of action currents or alternation of both purposes by means of a simple switching apparatus.

In both cat and man the typical cortical alpha wave appears 10 per second and about 50 to 70 microvolts in amplitude. Hypothalamic waves appeared in a much slower rhythm, only 4 to 5 per second and were about 75 per cent of the amplitude of the cortical waves. Superimposed on these were minor, tiny, 13 per second waves. Into the normal resting hypothalamus, cortical rhythm often permeated, resulting in an alpha type of wave which was less regular, lower in amplitude and often receding and recurring. Destruction of the tissue to the point of extinction of the hypothalamic waves allowed the cortical alphas to become clear, frequent, and of usual amplitude in the hypothalamic lead. Cortical rhythm thus enters into the normal resting hypothalamus but dominates it only when the hypothalamus is injured. The resting human hypothalamic pattern seems to be more individual to a given person than his cortical pattern and may represent a valuable constitutional characteristic. On the other hand, it may be a correlate of his psychological phenotype and hence partially alterable. This is a problem worthy of study.

Stimulation through the hypothalamic lead in man produced the well known general visceral effects on blood pressure, respiration, pupils, heart rate, sweating, vasomotor tone, bladder and body temperature. Each of these functions may be studied further through this mode of stimulation with the use of appropriate measuring instruments, i.e., electrocardiograph, gastroscope, cystoscope, capillaroscope, etc. Additional evidences of excitatory effects were clinically observed in the emotional reactions of the patients. Frequently they showed profound anxiety. In one, protracted uncontrollable sobbing occurred, another felt his life pass before his eyes, another felt the end of the world approaching. These subjective reactions require further detailed study. In no patients were emotional expressions of anger noted; all responded with fear. Stronger currents elicited tonic and sometimes clonic movements of the extremities comparable to the running or clawing movements of Ranson's cats.

The objective result of stimulation of the hypothalamus was excitation. The effect on the hypothalamus itself was a marked increase in fast waves and disappearance of the cortical alpha rhythm. The typical 4 per second waves became irregular and often doubled in amplitude. A new type of wave consisting of coarse undulations, 70 per minute and of only 30 microvolts in amplitude, appeared. Giant waves interrupted the rhythm for several seconds at a time. After strong stimulation, the hypothalamic rhythm—this was true in the cat also—synchronized with that of the cortex. The late effects of stimulation on the hypothalamus itself were striking. The 70 per second rhythm receded and reappeared. The giant

waves often disappeared and were replaced by a modified 10 per second alpha rhythm interspersed by large round slow waves at 2 per second. These faded and returned; also large spikes and cusps appeared for one or two seconds to disappear again in a quiescent phase. An occasional train of fast waves also appeared. Thus, after the initial excitation, short recurrent irregular waves of heightened hypothalamic activity reappeared.

The cortical objective responses to hypothalamic stimulation were equally striking. Large rounded waves 100 to 150 microvolts in amplitude, appearing once in 2 or 3 seconds, were seen. These appeared sporadically for several minutes after cessation of the stimulation. Large wavy undulations appeared in the curve, gradually becoming lost after several minutes. Spikes of 100 or more microvolts, appearing 4 per second in the characteristic hypothalamic rate, often appeared in phase with large rounded waves in the hypothalamus in bursts lasting 4 to 5 minutes after stimulation. After stronger and longer stimulation large series of giant round waves appeared in an identical form to hypothalamic waves of excitation, and in synchrony with bursts in that region. Alpha waves were slowed to 5 per second and often intensified to as much as 400 per cent. Giant waves as high as 250 microvolts appeared in groups and isolated, often erupting as a late effect in the midst of a normal alpha rhythm.

Drugs which act upon the central autonomic nervous system were injected into animals and simultaneous action currents from the hypothalamus and cortex recorded. Their effects may be briefly described, only to show that a pharmacological effect on the hypothalamus secondarily influences the cortex similar to electrical stimulation.

Adrenaline produced a strong excitatory effect on the hypothalamus accompanied by a vigorous cortical response in the same direction, similar to strong electrical stimulation because synchrony with preponderance of the hypothalamic pattern was observed. Eserine produced a transient excitatory effect on the hypothalamus with a much more prolonged effect on the cortex, which is of interest in view of its capacity to inactivate choline esterase which destroys the parasympathetic hormone, acetylcholine. Metrazol evoked a rapidly passing excitation of the hypothalamus. Each of these drugs caused a hypothalamic excitation and influenced the cortex in the same direction. Thus, the cortical effects from hypothalamic electrical stimulation are probably the result of excitation of the orthosympathetic centers in the hypothalamus.

Ergotamine resulted in a hypothalamic excitation but inhibition of the cortical currents. This drug is an orthosympathetic paralysant and thus its effects on hypothalamus probably liberated parasympathetic responses. Nembutal caused a slowing of both hypothalamic and cortical action currents which is interesting in view of the now widely accepted idea that barbiturates exert their hypnotic effect by primarily quieting the orthosympathetic centers in the hypothalamus. Pilocarpine caused a marked paralysis of both hypothalamic and cortical responses accompanied by signs of parasympathetic stimulation in pupillary constriction, sweating and salivation. Its effects on the parasympathetic centers of the hypothalamus were opposite in direction to orthosympathetic excitation, slowing and decreasing cortical activity.

Parasympathetic excitants and orthosympathetic paralysants show a reversal of changes to those exhibited by electrical stimulation. Thus pharmacological experiments indicate clearly the antagonistic effect of the two divisions

of the central autonomic centers in the hypothalamus on cortical activity.

Our next experiments were concerned with biological stimulations while hypothalamic and cortical currents were registered. Strongly emotionally-laden ideational stimuli were used. A patient with large amounts of free-floating anxiety loosely related to masturbation was told of the bad results which might accrue from the habit. The resulting hypothalamic and cortical excitation was similar to that described from electrical stimulation. The late recurring bursts of increased activity and the coarse disintegrated appearance of the curve were also noted as well as irregularly appearing synchrony in the two leads.

Since these experiments are at present the only available objective evidences of the effect of hypothalamus on cortical activity, they may be discussed briefly. The combined results from electrical and pharmacological effects indicate that the hypothalamus excites cortical activity through its orthosympathetic centers. The apparent mass effect of electrical current through the bone eventuates in orthosympathetic predominance. This has been found true in animal experiments; orthosympathetic responses tend to overweigh those of the parasympathetic type. This excitatory effect on the cortex in our experiments is identical to the excitatory effect of emotionally-laden verbal stimuli. Finally, the effect of such electrical, pharmacological and biological stimuli are homologous to the general excitatory effect that stimulation of the lateral hypothalamus has on peripheral organs of emotional expression, and orthosympathetic paralysants through the hypothalamus elicit cortical responses similar to destructive lesions of the posterior hypothalamus.

The resting hypothalamus has a typical pattern in which cortical elements enter weakly. After weaker currents both hypothalamus and cortex are excited. Stronger currents elicit a synchronization of cortex and hypothalamus in which the pattern of the latter is dominant. When a certain excitation is reached a mass activity of cortex probably results, homologous clinically probably to impulsive unconscious actions such as flight, impulsive suicide or "blind" attacks of rage. Cortical dominance is lost and hypothalamic "mania" dominates the picture. Certainly our results objectively indicate the assumption that emotions influence intellectual processes through the mechanism of hypothalamus driving the cortex.

The repeated long prolonged bursts of excitation in hypothalamus and cortex indicate that the hypothalamus does not discharge always at once, but acts as a reservoir exerting a chronic effect on periphery and centrum. Emotional stimuli given once caused the same prolonged discharges which gradually became feebler. Clinically this phenomenon is homologous with the recurrent "popping up" of unpleasant ideas which the subject attempts to suppress.

There are many problems which can be attacked by this method. Is the functional hypothalamic pattern alterable by means of deep psychological analysis or is it a fixed constitutional factor? The specific differences in the pattern in certain personality types, in various moods and in diverse mental and emotional disturbances should be determined. Furthermore, stimulation of the hypothalamus in the human has a therapeutic possibility in depressions, stupors and perhaps schizophrenia. Stimulation of the hypothalamus directly should influence the autonomic functions which are only indirectly influenced by metrazol and insulin. With the same idea in mind Cerletti and

Bini (*13*) treat schizophrenics by means of convulsions produced with electric shocks, which, however, are generalized and not in the form of specific induction shocks to the hypothalamus. They report results as good as those obtained from pharmacological shock.

VII. Hypothalamus in Mental Disturbances

Clinical disturbances of the hypothalamus due to tumors of the parasellar region pressing on the base of the third ventricle have been reported in abundance (*36*). Bailey and Murray (*5*) studied a 15 year old boy with a pinealoma who had symptoms of an obsessional neurosis for which he was treated. The patient had a compulsion for drinking water which, unlike diabetes insipidus, was not relieved by the administration of pituitary hormone but was improved by incarceration of his father in a reformatory. Psychological study of the case clearly indicated the dynamic mechanisms and yet at necropsy the neoplasm had involved the hypothalamus. Schilder (*75a*) has recently indicated that some compulsive neuroses have an organic foundation in chronic encephalitis which we know has a predeliction for the diencephalon.

Gagel (*28*) pointed out that emotional changes were the most constant symptoms of hypothalamic disturbances due to tumors. These symptoms were either in the nature of euphoria or mania (*75*). Foerster and Gagel (*21*) reported one case and since then Foerster has had several cases on whom electrical stimulation of the exposed human hypothalamus was performed at operation. The result of stimulation of the anterior hypothalamus was restlessness, excitement, euphoria and mania, which could be elicited from stimulation of no other locus. Stimulation of the mesencephalon and posterior hypothalamus produced sleepiness and unconsciousness. These authors believe that cortical functions are influenced by the hypothalamus in that they are excited and stimulated from the oral part and inhibited from the posterior portion.

In the literature there are many cases of euphoria, mania and mental excitation from suprasellar neoplasms arising from epithelial cysts of Rathke's pouch (*8*, *78*, *66*). Fulton and Bailey (*27*) in their reports of psychomotor excitation and mania from tumors of the third ventricle go so far as to deny any psychogenic bases for these symptoms. The maniacal delirious state in Korsakoff's syndrome has also been correlated with lesions around the third ventricle (*61*). Cases of maniacal excitement in encephalitis of childhood are associated with hypothalamic lesions. Bender (*10*) made anatomical studies of alcoholics with disturbances of consciousness and felt that in the region of the third ventricle there were centers concerned with awareness. Neurosurgeons have come to the conclusion that the anterior part of the diencephalon is somehow related to depth of consciousness. Manipulation of this region often results in loss of consciousness with hyperpyrexia. Grotjahn and French (*34a*) report seven patients with lesions of the hypothalamus who developed severe akinesia and showed evidences of dissociation between the cognitive and volitional aspects of the ego's synthetic activity.

Alpers (*3*) reported three cases of disorders of personality, one due to a verified tumor in the third ventricle. Megalomania, disorientation, irritability, facetiousness and argumentativeness were characteristic. In another case, long standing disorientation was described; in another excitement, hallucinations and combativeness was re-

sponsible for the erroneous diagnosis of manic depressive psychosis. Horrax and Yaskis (*42*) report manic depressive symptoms relieved by removal of an intradural cholesteatoma.

Gagel (*28*) summarized the hypothalamic syndrome as follows: The patients are coarse and show a loss of inhibitions and lack of niceness in behavior and of ordinary social courtesies. Many patients are irritable and hypersensitive and show loss of judgment. They have attacks of rage and swings of mood. Memory changes and quantitative reduction in intelligence appear late.

In the so-called endogenous, manic-depressive psychosis an affective disturbance exists which is identical with variations of mood described as the result of hypothalamic lesions. Patients are slowed, retarded, depressed with difficulties in thought, attention, etc., or they are gay, euphoric or maniacal with great psychomotor excitement. The primary disturbance involves the direction and extent of the mood, yet the effect on thinking is obvious, indicating, as the natural experiments of disease and the animal and human experiments previously described, the great effect of hypothalamic activity on cortical functioning. The absence of an organic disturbance demonstrable by our present technical means and the complete reversibility of the affect indicates a functional disturbance which, in producing the same symptoms as organic lesions or experimental excitation, probably utilizes the same anatomical mechanisms.

Morgan (*62*, *64*) studied the diencephalic regions in certain cases of dementia and psychoses and found degenerative changes and reduction of volume in the substantia grisea of the third ventricle. There was no difference as to the site of the lesions in excited or deteriorated cases. This work requires rechecking. Fünfgeld studying the neuropathology of schizophrenia found changes of significance in the hypothalamus and according to him and Kleist, personality is a function derived from activity of the diencephalon, truly a neurologizing of psychology.

Ingham (*43*) clearly summarizes the general impression of localization of consciousness in the hypothalamus:

> The neurologic concept of consciousness is that it is a state of activity of the entire nervous system, and in particular of the brain, which varies quantitatively from the maximum degree of mental action to complete inactivity, as in coma or general surgical anesthesia. Although all parts of the brain may contribute to the mental processes during consciousness, mental activity of all kinds appears to depend on the normal functioning of groups of neurons in the primitive diencephalon. The normal cycles of sleeping and waking are evidences of the physiologic activity of this mechanism. As it would appear that energy liberated in the diencephalon is essential for the activation of all the rest of the nervous system so far as psychologic phenomena are concerned, it may be postulated that the "center" of consciousness is located in this region, and much clinical and experimental evidence supports this view. It is surely not accidental that other primitive functions of the nervous system related to the vegetative processes, instincts and emotions have been found to be dependent on structures in the basal region of the brain in close proximity to those postulated as the center of consciousness. The application of this concept of consciousness to psychiatry seems obvious, since quantitative variations of consciousness are manifested in disturbances of behavior in terms of intelligence, emotions and instinctive action.

Jelliffe (*46*, *48*) stated that the disease epidemic encephalitis created a new orientation toward the mental and emotional life of man by indicating the close relationship between disturbances of the autonomic nervous system and behavior reactions, sleep disturbances

and rage attacks. Jelliffe (*47*) pointed out the similarity between epidemic encephalitis and schizophrenia. In chronic encephalitis there are all gradations of affective reactions including placid optimistic states, trance-like phases, tetanoid, epileptoid, narcoleptic, cataleptic, catatonic and stuporous states. In the chronic stage of encephalitis all combinations of disturbances of hypothalamic function are observed including alterations in metabolism, autonomic regulation, degree of awareness or depth of consciousness and in emotional states. Unfortunately these effects are never pure and the morphological alterations are not limited to the hypothalamus so that anatomico-physiological correlations cannot be made. Yet these symptoms have indicated clearly how the hypothalamus in man is so vitally concerned in feeling attitudes and in what Head (*38*) has termed "vigilance".

Grinker (*31*), discussing the relation of cortex to hypothalamus in the production of human symptomatology, stated:

> It is not impossible that either anatomical or functional (cytochemical, etc.) lesions of the hypothalamus or its connections with the cortex may cause complete or partial release of cortical (ideational) control of the emotional content of higher activities. The dominant external activity would then be, not a slow adaptive response produced by a process of long-circuiting but a less deliberate (impulsive) response with accompanying visceromotor correlates of emotional reactions.

There is, however, equal evidence for the assumption that clinical symptoms referable to the hypothalamus are due to excitation rather than to release of its control by the cortex. The mechanisms involved in release must be more significant in the causation of hypothalamic overactivity of psychologic origin in the psychoneuroses.

A relationship of disturbances of the central autonomic nervous system to schizophrenia has for long been suggested by many observers. The central autonomic nervous system, regulating and integrating the quantitative output and direction of flow of energy and the forcefulness of a person's active adjustment, is probably concerned with the production of mental disturbances. True schizophrenia is to Singer (*77*) due to a structural lesion of the autonomic nervous system. His co-worker Gellhorn (*29*) believes that the physiologic beneficial effects of hypoglycemia and metrazol are achieved by stimulation of the autonomic centers which function deficiently in these patients.

Many workers have carefully studied visceral functions in schizophrenia. The literature contains numerous reports indicating a relatively mild deficiency of basal metabolism, oxygen consumption, hypoplasia of smooth muscle and many visceral activities, suggesting a deficiency of the function of the autonomic nervous system in schizophrenia. However, there are many conflicting observations, as the negative studies of Freeman and Carmichael (*22*) indicate. Finkelman (*19*) most recently reported a low heat production in response to cold and a poorly maintained heat production with no reactive hyperemia in schizophrenics, which he thought might be due to a hypothalamic disturbance. In schizophrenia, deficiencies in the autonomic nervous system are less under basal states, or conditions of ordinary maintenance, than under *stress* during which normal reactive processes fail.

The biological data resulting from studies of schizophrenics suggest strongly a deficiency in some central autonomic coordinating process, mirrored clinically in defective homeostasis. There is also evidence from the psychological side that schizophrenics

are incapable of adequately solving, with their psychosomatic constitution, the problems of frustration and separation that the bare act of living within a restricting society creates. Their visceral cravings or instinctual demands are of such strength that inhibitions are overridden, compromise rejected and autonomic drives overwhelm the cortex, destroying ego functions. The strong urge to cling to the all protective embracing mother and the marked rage evoked at separation, are far and beyond that seen in any normal. The strong wish to return to the womb with its sunlit rooms where existence requires no autonomic adjustments is dominant.

The difficulty that the schizophrenic has in relieving his tensions partially or symbolically in adaptation increases to a point where cortical inhibitions, conditioned by the adaptation-demanding reality fail, and hypothalamic activity forces itself into direct expression. The results are violent emotional outbreaks or, physiologically speaking, cortical activity under direct control by the hypothalamus. In this connection it is interesting to note that when emotional activity or hypothalamic excitation reached a certain height in our experiments, cortical activity, as indicated in the electrogram, became coarse, irregular and of the hypothalamic pattern. In this phase the cortical curves resemble the disorganized curves found in clinical schizophrenia with excitement and over-activity.

Other types of schizophrenia show, during basal conditions, coldness of the extremities, slowed respiration, low blood pressure and decreased metabolic rate indicating defective homeostasis at *rest*. We may postulate that in them the visceral tensions are decreased and the driving power of the hypothalamus is reduced to the point where cortical activity is not maintained. We may postulate that these patients range from the schizophrenic stupors to the dull so-called deteriorated types and in them the brain waves resemble those found in organic disease of the cortex. Regression has extended to a much lower level.

The above considerations concerning the rôle of the hypothalamus in mental disturbances are for the most part speculative. The positive facts are that stimulation of the hypothalamus produces excitement, restlessness and mania and an increased activity of the cortex; destructive lesions produce the opposite effect. These variations of effect are probably homologous to excitation of what in the normal individual functions as a center of awareness, the inhibition of which results in sleep. Pathological variations in its activity result in mania, on the one hand, and stupor, on the other. Functional or constitutional disturbances of such an anatomical hypothalamic-cortical mechanism are possible explanations of psychogenic variations in mood and alterations of cortical activity found in the so-called functional psychoses.

VIII. Psychosomatic Implications

In the early days of psychoanalysis interest in conversion phenomena was mainly directed to hysterical paralyses, anesthesias and pains. The "mysterious leap from psyche to soma" that attracted most attention were alterations of function in structures innervated by the voluntary nervous system. However, gradually interest veered to symptoms which were produced by disturbances in the autonomic nervous system and it was then not long before psychiatrists turned full attention to what Freud in the last decade termed the "future of medicine". At the present date psychoanalysts are busy studying the psychogenesis of peptic ulcer,

mucous colitis, spastic bowel, hypertension, bronchial asthma, diabetes mellitus, eczema, arthritis, migraine and a host of other conditions hitherto segregated from psychiatric interest because of their supposedly organic causation.

It was Alkan (*2*) who first clearly stated that organic disease may be profitably studied by psychological methods. He indicated that psychogenic disturbances within the field of the autonomic nervous system may result finally in organic changes, the morphological mechanisms of which form only the last link of an intricate causal chain. He postulated that intrapsychic conflicts may be expressed by spasms of smooth muscle which secondarily lead to anemia of an organ, stasis, muscular hypertrophy or infection. As a result of these secondary factors, organic changes result in the visceral tissues or somatic structures which of themselves, as terminal events, are irreversible and constitute the so-called organic disease.

Independently, Alexander (*1*) was convinced of the psychogenesis of, at first, gastro-intestinal disorders, later, respiratory and vasomotor disturbances through his psychoanalytic researches. He believes that organic changes are the last link in a complicated function chain of events, the basic etiological factors of which are psychological conflicts. His analyses led to more detailed statements concerning the specific emotion on which the organ neuroses are based. This accomplishment depended upon a general methodological principle entirely different from the vague application of the never fully accepted freudian death instinct. By the latter method as applied by Menninger (*59*), who fully expressed his thesis in the title of his book "Man Against Himself", organic disease is but a manifestation of self or internally directed aggression or death instinct which results in focal or partial self-destruction. Thus, to Menninger, the organ disturbed or the mechanism of its disturbance represents symbolically the repressed emotionally-laden idea.

Alexander, however, states that no disturbance of innervation of an organ could symbolically express a specific fantasy or a repressed idea. On the other hand, an organ's specific function could be used to express a tendency or psychic direction which by a process of conflict could not normally be expressed through the voluntary nervous system and its organs of expression. Analyzing the psychological vectors it was possible to show that:

> Physiologically the process of life can well be described in terms of the three major functions of *in-taking* of substance and energy from the environment, partially *retaining* it during the process of growth, and *elimination*—elimination of the end-products of products of metabolism, elimination of substance for the purpose of propagation and the constant production of thermic and mechanical energy. It would not be surprising at all if it should turn out that the most elementary psychologic tendencies of the individual correspond to these three biologic phases of life, and that psychologic dynamics . . . correspond to the biologic dynamics of life.

Why certain individuals choose a specific physiological solution for their conflicts is the unsolved field of the "choice of the neurosis" and Alexander assumes the answer probably lies in some unknown organic factors which, in cooperation with psychic factors, leads to the organ neurosis. The organ neurosis is then, primarily the abnormal use or innervation of an organ in an expression of a repressed tendency, thus disturbing its function. The disease is the end-result of the abnormal function.

Dunbar (*17*) collected a wealth of data regarding psychosomatic interrelations and clearly indicated the extent of the field and the possibilities of further study. Her analysis showed the importance of a more complete understanding of the position of the autonomic nervous system and its regulative centers in the effector role of emotional expression in normal and conflictual situations. According to Grinker (*34*), in order to understand the role of the autonomic system in the so-called functional disturbances in which regressive infantile modes of emotional expression are utilized, the processes of evolution and so-called normal development must first be understood.

Hughlings Jackson (*79*) considered that the nervous system was developed gradually into an hierarchy in which several definite levels could be discovered. His main interest was with the anatomico-physiological scheme of the somatic nervous system which, however, is equally valid for the autonomic nervous system. Jackson's centers or levels of evolution consist of 1) the lower motor centers in spinal cord, medulla and pons; 2) the middle level or motor and sensory cortical regions, and 3) the highest motor (prefrontal) and sensory (occipito-parieto-temporal areas of Wernicke's zone) centers of the cortex. The higher the level the more indirectly it represented the body and the more complex and numerous it could effect combination of the parts which it represented.

This evolutionary principle of gradually developing levels is concomitant with the principles of encephalization, according to which functions wander toward the head end or higher levels of the organism, newer functions are attributes of newer more cephalic developed structures, and older more primitive functions of lower centers are inhibited by dominance of cephalic segments over caudal centers. In this way most functions are represented at all levels, some are specific to certain levels, but all are dovetailed by higher dominance to effect smooth-working function. When higher centers are damaged or disturbed lower centers act alone and uninhibited, and their excessiveness furnishes the positive aspects of disturbed function, while the negative aspect is only the loss of function exclusively resident in the disturbed tissue.

According to Fulton (*25*):

> Newer disclosures concerning the relation of the cerebral cortex to the autonomic system give an adequate physiological basis for the relationship long recognized between mental states and visceral processes. To be a little more specific, it is clear that one now has adequate reason for believing that the load which is placed upon the heart and circulation may be determined in large measure by the mental status of the individual, and be thus quite independent of the more obvious factors of over-exercise and exertion. The heart and circulation may be worked just as hard, and just as much as a detriment to the body as a whole, from the swivel chair as from a rower's seat. Many disturbances of gastro-intestinal functions undoubtedly have a similar basis, and one might add that instead of referring to them as "psychogenic disturbances" one may more appropriately designate them as purely physiological aberration and explicable in terms of recognized physiological mechanisms. The more precise analysis of these psychosomatic relationships will come from the study of man and hence can only come through active collaboration between clinician and physiologist.

Fulton's thesis postulates that positive mental and emotional states, concomitant with activity of the cerebral cortex, are accompanied by visceral changes also arising from cortical excitation. According to this theory, the

visceral changes are secondary to the mental state or neurosis, but most of our psychological data suggest that the visceral activity indicates a concomitant psychological vector and that the neurosis is both the mental and visceral change. They cannot be separated and neither is cause nor effect; at least such is our concept in psychosomatic medicine.

It is difficult to homologize levels of the autonomic system to the Jacksonian somatic levels because its peripheral ganglionic system, central representation, and its dual divisions of para- and orthosympathetic divisions which are mutually antagonistic. However, it is suggested that the visceral ganglionic system, spinal medullary and pontine centers comprise the lowest level; the hypothalamus and cortical areas which are adjacent to the cortical motor centers, and premotor areas as the middle level; and the hippocampal formation and gyrus cinguli (perhaps others) as the highest level. As in the somatic nervous system the highest levels not only add new functions and take over in more complex form older functions from lower centers, but they also inhibit and damp down the functions of these lowest centers (*34*). In disease states the function of the lower centers are released and, in their then excessive action, comprise the major portion of the symptomatology. For example, cortical ablation in its production of "sham rage" has released from cortical control hypothalamic orthosympathetic functions which then are excessive and represent a caricature of normal activity.

Higher activity means of course inhibition of lower, more rapid, intrasegmental and simpler reflex functions; there occurs a long-circuiting of impulses to higher segments. What are these simpler autonomic functions and their psychic concomitants? They are based upon simple visceral functions of intaking, retaining and eliminative functions innervated by the autonomic nervous system and are the only means by which the immature infantile nervous system expresses its feelings. The concomitants of these functions represent its emotional life. As development occurs the instinctual drives and tendencies are long-circuited to higher cortical centers where they are normally symbolically formulated and discharged as, at the same time, the simple visceral expressions of emotion are inhibited.

Hence the highest level has added the new functions of 1) synthesis of perceptions and 2) discharge in symbolic expression but also 3) damped down lower orders of responses and reactions to stimuli as individual excitations. These new functions are cortical and correspond to the psychological ego which synthesizes and discharges.

In excessive psychological excitation, passing beyond the capacity of the ego for symbolic discharge, in which the pressure of instinctual drives meets resistances, ego functions become fatigued or paralyzed. There result two aspects as of any lesion. The negative aspect is evidenced by the fact that the instinctual drives are not expressed through the highest level in highest symbolic expression. There is a hole in cortical activity which, however, is not a gaping wound through which psychic material readily flows. It is a nonconducting gap. The positive aspect or so-called "return of the repressed" is a symptom which bears evidence of regression, for the push toward activity must find its expression through lower levels now permitted to act by release due to the absence of higher inhibiting functions.

Psychoanalytic theory of symptom-formation implies that the repressed or undischarged energy must escape else-

where than through the motor activity of the ego—that it returns modified as a symptom. The same phenomenon has been described by Pavlov, for when reflexes are inhibited from one skin area, they are increased elsewhere. In neurological terms, Jackson stated that diminished action in one part of the nervous system results in exalted action in another part, but this so-called new action takes place on a lower level. Neurologically, release of lower levels results in a greater preponderance of visceral participation in reflex activity and, psychologically, alloplastic reactions are replaced by autoplastic innervations. Innervations engage organs whose functions represent the level of psychological activity to which the psychic life has regressed, thus producing sucking, biting, soiling and retaining psychologically, as Alexander has shown in his vector analyses. Thus, functional innervations of various appropriate organs, released from inhibition, set into effect the first link in the causal chain of events that end in visceral disease. Regression in the psychoneuroses and organ neuroses probably does not extend lower than the hypothalamus. Evidence of preservation of its integrating function in the visceral systems and personality indicates its intactness.

The problem of choice of regressive symptoms remains, however, as obscure in a physiological analysis as in a study of the emotions. Isolated hypertension, decreased peristalsis, etc., are difficult to explain psychologically, since the orthosympathetic centers in the hypothalamus act in unison to evoke mass reactions. From the work of Schou (*76*) with the minor emotions, it seems possible that more than an isolated visceral function is disturbed and it is suggested that the entire autonomic nervous system be investigated in these cases. Parasympathetic disturbances and endocrine symptoms of the parasympathetic group such as diabetes, adiposity, genital disturbances, vasomotor changes, gastro-intestinal hyperfunction and ulceration are, as we have seen, much easier to understand as isolated physiological responses.

Differing from the schizophrenics in whom the tension of the autonomic nervous mechanisms cannot be diminished, expressed symbolically or only partially, the organ neurosis probably represents a graded release of inhibition from the cortex. In the schizophrenic visceral tensions become too powerful; in the organ neuroses our hypothesis considers that the obstacles and difficulties of reality, conditioned by specific frustrating experiences, become too strong and the resulting fatigue of a focal area of the cortex releases its control over the lower centers. The result is a shunting of expression through direct visceral activity in a regressive manner instead of in a long-circuited symbolic expression.

IX. General Considerations

Before attempting the following dynamic speculations it must be repeated that the hypothalamus was primarily a precipitate within the olfactory system in a region from which central autonomic structures developed. It became a primitive center for olfacto-visceral correlation. In 1934 Grinker (*31*) wrote:

> Just as in the diencephalon, with its numerous olfactory interconnections, the great bulk of apparent olfactory and gustatory fibers in the hippocampal structures seem all out of proportion to the insignificance of these functions in man. Perhaps evolutionary processes have not yet atrophied this previously important structure. I should surmise, however, that much of the olfactory system is no longer subserving

its original function, but may be concerned in more evolved, perhaps higher, autonomic functions. Herrick (*39*) suggests, for example, that the olfactory cortex may maintain a tonic influence on the neopallium, perhaps important in the function of learning.

Papez (*68*) recently wrote in the same strain. He states that the great sensory station within the thalamus gives rise to three great pathways. These converge 1) to the striatum which constitutes the stream of movement, 2) to the cortex or the stream of thought, and 3) to the hypothalamus-gyrus cinguli unit as the stream of feeling. He believes the latter gyrus receives impulses from the hypothalamus which evoke emotional feelings, then influencing other cortical areas. According to Papez (*38*) the gyrus cinguli constitutes the cortical center for dynamic vigilance, for tumors in its neighborhood are associated with apathy and drowsiness. This agrees with Herrick's (*39*) concept of olfactory cortex exerting a tonic influence on the cerebrum. The hippocampal portion of olfactory cortex in man is also probably largely concerned with emotional feeling, for therein are found the negri bodies in rabies, a disease in which insomnia, irritability, restlessness and fright are so striking. In this connection Klüver's recent extirpation of both temporal lobes in monkeys is important, for the experimental animals exhibited no normal expressions of fright or anger.

Since any discussion of the hypothalamic mechanism includes consideration of emotion, it is well to turn to its definition. All concepts of emotion are concerned with energy either in action or symbolism. McKinney (*60*) in paraphrasing Spinoza formulated the following definition: "By emotions I understand the modifications of energy by which the power in action of the body is increased or diminished, aided or restrained and at the same time the ideas of these modifications".

Concerning the argument regarding the peripheral or central origin of emotions we need concern ourselves little (*73*). *Emotional expression* is always peripheral and one cannot deny that it may reverberate and amplify the central feelings. To express the idea that *emotion* is of peripheral origin is to forget the evolutionary significances of central structure and the processes of encephalization. The developed human may express his feelings symbolically with a minimum of visceral accompaniment, yet in certain conflictual situations regression may release peripheral expressions and re-evoke old patterns. The amount of such regression is probably one quantitative factor in the neuroses.

As a cephalic representative of the autonomic nervous system, the hypothalamus has to do with energies of visceral origin which are the forces of the instincts. It controls activities of the periphery in metabolism, balancing the constructive and destructive tendencies, and it forces activities of the cerebral cortex. It represents tensions or "cravings" within the autonomic system (instinctual) which are precipitated and coordinated in the hypothalamus rather than expressed individually and incoordinatedly. Its transmitted tension stimulates activity within the somatic nervous system, including the cerebral cortex, into a search for adequate stimuli (food or sexual), which stimuli release tensions and end in visceral quiescence.

Evolutionary development took away from the hypothalamus its dominant role in emotional expression during the processes of encephalization. Instinctual cravings become synthesized and formulated in a slower acting more adaptive structure in which the processes of conditioning, or learning

by experience, dominate rapid reflex action. To achieve these slower adaptive responses the hypothalamus became subordinated to higher newer cortical centers by inhibitory processes emanating therefrom. The hippocampal-cinguli formation, subserving the conscious sensation of emotion revalued in relation to other cortical functions, also damps down hypothalamic excessive responses and allows only mild peripheral activities to be carried on in economically graded form, avoiding excessiveness.

However, in turn the hypothalamus influences activity within the cortex or ego. Its drives are synonymous with id demands or necessities of the instincts. This is represented clearly in the hypothalamic influences on the cortex in sleep, wakefulness and consciousness, which represent modulations of drives called emotional. There is postulated, then, a mutually antagonistic system with cortical inhibitory influences predominating in most spheres. A phasic release of such inhibition results in appropriate centrally directed visceral responses and graded emotional expressions. Cortical inhibitions are, however, directed by learning or conditioning involving ego functions. Psychologically we are justified in assuming that such inhibitions or releases are directed upon the ego by environmental or social forces or their intrapsychic incrustations. Freud (*23*) spoke of all this when he stated that the ego served three masters: reality, the super-ego and the id.

The emotion of anger is teleological in that it results in the stimulus being removed from the receptor. Fear removes the receptor from the stimulus and flight occurs from a real danger. In anxiety, however, the danger is not real, it is unknown, internal, and results from an increase in instinctual tension demanding expression. As Freud (*23*) points out, it is a conditioned signal within the ego, conscious within the personality as a warning of impending danger. There are specific unpleasurable feelings, efferent discharges and their perception. The result may not be fight or flight, as to a real danger, but a paralysis of certain higher ego functions. Anxiety is then the first sign of an autonomic influence on the cortex or ego, which has been learned by previous testing to indicate danger for the organism. It is a feeling which accompanies autonomic forces sufficiently strong to overcome cortical inhibition and force the cortex into activity, movement resulting in an attempt at solving the situation which has evoked the internal tension. Psychological fight or flight or compromises are attempted. Often successful solutions are not possible and the cortex or ego "gives up", allowing regressive and infantile modes of exteriorization of emotional expression, for the sake of avoiding more prolonged or greater emotional feelings. The result is visceral expression or organ dysfunctions, which we term organ neuroses, that constitute the first step toward organic disease.

X. References

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THE HYPOTHALAMUS: A REVIEW OF THE EXPERIMENTAL DATA

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THE GENERAL STRUCTURE OF THE HYPOTHALAMUS

THE HYPOTHALAMUS comprises a relatively small area on the ventral aspect of the diencephalon, forming the floor and portions of the walls of the third ventricle. It is delimited dorsally from the thalamus proper by the hypothalamic sulcus and may be said to extend rostro-caudally between the anterior border of the optic chiasma and the interpeduncular fossa. It is bounded laterally by the internal capsule and the subthalamic structures. Grossly its ventral aspect presents the bulging tuber cinereum, the mammillary bodies and the infundibular or hypophyseal stalk which unites the pituitary body with the brain. While the caudal, lateral, and dorsal boundaries are quite obvious, the rostral one is not so clearly defined and the substance of the hypothalamus blends with that of the so-called preoptic area, which in itself may possess some of the functional attributes of the hypothalamus.

It is convenient to divide the hypothalamus into three areas, the supraoptic, tuberal and posterior (Beattie, *20*, 1932). In the supraoptic region, dorsal to the chiasma, are several important nuclei represented bilaterally. The supraoptic (sometimes called the tangential), lies over the beginning of the optic tract and is composed of large cells which stain heavily with the commonly used blue dyes. This nucleus gives rise to nerve fibers extending to the hypophysis. Along the wall of the third ventricle dorsomedial to this group is the paraventricular (or filiform) nucleus, which is composed of similar cells. The anterior hypothalamic nucleus is a sometimes poorly defined group of smaller cells imbedded in the diffuse gray matter dorsal to the chiasma. The nuclei of this and more caudal areas lie in a mass of gray matter called the substantia grisea hypothalami which contains neurons of various sizes, chiefly small. Two other smaller nuclei are the periventricular and the ovoid. Dorsal and lateral to the supraoptic nucleus is an area containing numerous unmyelinated and small myelinated fibers of the medial forebrain bundle, in which are embedded numerous small neurons and a few large ones. This is the lateral hypothalamic area, a functionally important region, bordered laterally by the internal capsule and extending caudally throughout the hypothalamus.

The tuber region, made distinctive by the infundibular outpushing, is a mass of gray in which several structures may be distinguished. The ventromedial nucleus, the most conspicuous group in this region, is a rounded mass of closely packed cells occupying the body of the tuber itself. Dorsal to it is the dorsomedial nucleus, less distinct, and closely associated with slender chains of small neurons lying among the fibers bordering the ventricle, the

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periventricular nuclei. In primate brains the lateral area contains 2 or 3 small round groups of pale cells, the so-called lateral nuclei of the tuber. The lateral course is traversed medially by the fornix.

The posterior hypothalamus is made conspicuous by the mammillary bodies. Each of these contains two main nuclei, a larger, pale-staining medial and a smaller, dark-staining lateral nucleus. Laterally and dorsally lies the nucleus intercalatus. The fornix enters chiefly into the lateral mammillary nucleus. Extending dorsalward from the medal nucleus is the mammillo-thalamic tract, an important landmark, for between it and the ventricle lies the posterior hypothalamic nucleus, said to be a chief source of periventricular fibers. Dorsal and rostral to the mammillary bodies are some small condensations of cells apparently of minor significance. The supramammillary decussation or commissure is of some importance because it may possibly contain efferent descending fibers from the higher hypothalamic levels as well as striatal connections, especially in lower mammals. The lateral hypothalamic area in this caudal region narrows down considerably because the fibers remaining in the medial forebrain bundle appear to pass into the mesencephalic tegmentum. It contains a considerable number of fairly large, dark-staining cells of different type than those in the mammillary complex—these cells have been designated collectively by some authors as the nucleus tubero-mammillaris.

Relatively few of the neurons of the hypothalamus are of somatic motor type. The majority contain finely granular Nissl substance in varying arrangements and have been considered by most authors as autonomic in type. The Nissl pattern is variable, and it has been repeatedly pointed out that many cells in this region may normally present a picture which in any other region might be considered as showing a chromatolytic degenerative reaction. It is said that many hypothalamic neurons, when examined with suitable cytological methods, show definite signs of secretory activity Collin (*55*, *56*, 1933), Florentin (*93*, 1934) Gaupp (*106*, 1935), Kappers (*185*, 1935), Peters (*294*, 1935), Scharrer (*337*, 1933) Scharrer and Gaupp (*338*, 1933), Roussy and Mosinger (*326*, 1934).

The fiber connections of the hypothalamus are not easily determined, because of the difficulty involved in any experimental approach. While there are some conspicuous myelinated fiber systems, histological preparations made with the silver methods disclose an all pervading mass of unmyelinated fibers, with few clearly discernible tracts imbedded in a sort of background feltwork. Even if it were possible to localize suitably very small lesions, the resulting degenerations would be hard to follow because of our lack of a good method for staining degenerating unmyelinated fibers. While much has been written concerning fiber connections in this region, the work has been largely based upon normal material, and even if distinct tracts are observed, it is difficult to determine the direction of conduction. Any statements made, no matter how positively, must be taken with considerable reservation and considered merely as a background for future work with more suitable methods. The most reliable information has probably been gained by stimulation experiments.

The most conspicuous myelinated connections include the fornix and mammillo-thalamic tract, whose connections with the mammillary bodies, hippocampus, thalamus and tegmentum are well known and need not be discussed. These old systems are primarily olfactory and have been con-

sidered by Edinger as part of a gustatory system. Experimentally, no light has been cast upon their functions, because animals may behave normally after they have been destroyed. The medial forebrain bundle, also probably primarily an olfactory tract extending from the preoptic and parolfactory areas caudalward, contains many fine myelinated fibers along with a heavy mass of unmyelinated ones. Since this bundle diminishes in size as it passes caudalward through the hypothalamus many of its fibers must end in the latter. A few fibers, especially unmyelinated components, continue backward into the reticular formation of the mesencephalic tegmentum, possibly constituting a descending efferent pathway from the hypothalamus. A portion of this bundle, from which autonomic responses are readily obtained, runs ventral to the fornix and has been designated by Krieg (*214*, 1932) as its subfornical component. A strand of myelinated fibers running dorso-lateralward out of the ventromedial nucleus to join this system was thought by Rioch (*322*, 1931) to be efferent and was called the hypothalamo-tegmental tract. However, the writer has observed this bundle to persist long after destruction of the ventromedial nucleus, which would seem to indicate that if it actually has any connection with the latter it must be an afferent one. There is some possibility that it may come from the fasciculus thalamicus or the fasciculus lenticularis. Some scattered myelinated commissural connections which may arise in part in the hypothalamus are observed posterior to the chiasma in what is probably Ganser's commissure and also in the supramammillary decussation. An ascending afferent myelinated bundle, the mammillary peduncle, is said by Papez (*285*, 1932) to arise in the ventral tegmental nucleus. It ends in the neighborhood of the mammillary body. Perhaps, also, it contains descending fibers arising in the nucleus intercalatus (Clark *52*, 1936). A few myelinated fibers appear to turn dorsalward out of the optic chiasma immediately after crossing to disappear in the neighborhood of the nucleus ovoideus. Pate (*288*, 1937) has reported that enucleation of the eyes causes atrophy of this nucleus.

The unmyelinated fiber bundle about which the most definite information is available is the so-called hypothalamico-hypophyseal tract, which extends down the hypophyseal stalk to end in the pituitary gland. This tract was first observed in the rat by Cajal (*39*, 1894) and has since been studied extensively in higher forms by Gemelli (*108*, 1906), Tello (*368*, 1912), Watrin and Baudot (*390*, 1922), Hoenig (*153*, 1922), Kary (*197*, 1924), Lewy (*227*, 1924), Pines (*300*, 1925, *301*, 1926, *302*, 1931), Maiman (*251*, 1930), Cushing (*63*, 1932), Bucy (*36*, 1932), Roussy and Mosinger (*326*, 1934, *327*, *328*, 1935), Sanz Ibanez (*334*, 1934), Greving (*116*, 1925; *117*, 1926; *118*, 1927; *119*, 1931), Stengel (*362*, 1926), Croll (*60*, 1928), Mogilnitsky (*269*, 1928), Espino Vergara (*84*, 1924), Laruelle (*219*, 1934), Jores (*179*, 1935), Takeyama (*366*, 1936), Fisher, Ingram and Ranson (*88*, 1935), Ingram and Fisher (*167*, 1936), Fisher, Ingram and Ranson (*91*, 1938). There is evidence that this tract exists in lower vertebrates, also. Its heaviest fiber component arises in the supraoptic nucleus, passes down the ventral wall of the stalk and ends largely in the pars nervosa of the hypophysis, in relation to islets of secretory cells of a peculiar type. When the tract is severed, the supraoptic nucleus degenerates and the pars nervosa atrophies. The function of this supraoptico-hypophyseal tract will be discussed later. It is fairly well established that the bundle as a whole, however, has other sources

of origin than the supraoptic nucleus. Greving (*119*, 1931) and Roussy and Mosinger (*326*, 1934) believe it receives fibers from the paraventricular nucleus, and there is some indication of loss of cells from the latter when the tract is cut. Some of its fibers seem to arise in the tuber region and Roussy and Mosinger (*326*, 1934) picture them as coming from a number of nuclei there. Experimental evidence in regard to the latter is difficult to obtain. The bundle as a whole may well be called the hypothalamico-hypophyseal tract with two divisions, the supraoptico-hypophyseal and the tubero-hypophyseal, the latter occupying chiefly the dorsal wall of the stalk.

As to the termination;—the bulk of the fibers of this tract end in the pars nervosa among the so-called pituicytes (Gersh *109*, 1937). Some of them end in the median eminence and stalk (Sanz Ibanez *334*, 1934), which also contain pituicytes. Some authorities maintain that some fibers terminate in the pars intermedia although they cannot be numerous, and according to Hair (*128*, 1938) a few enter the pars tuberalis and pars anterior in the cat. It is very difficult to follow fibers from the hypothalamico-hypophyseal tract into the pars anterior. However, Brooks (*32*, 1938) was able to demonstrate nerve fibers in the anterior lobe of the rabbit after sympathetic sources had been removed; these fibers could not be found after section of the stalk, which is indirect evidence of their origin in the hypothalamus.

The main origin of the supraoptico-hypophyseal tract now seems well established, as the supraoptic nuclei have been repeatedly observed to show degeneration when the tract fibers are interrupted or the hypophysis removed (Kary *197*, 1924, Kijono *208*, 1925, Biggart *25*, 1936, Maiman *251*, 1930, Ingram and Fisher, *167* 1936, et al). Gagel and Mahoney (*104*, 1933; *105*, 1936) have denied that any such thing occurs but the weight of evidence seems against them (Rasmussen *317*, 1937, Hare *131*, 1937, Magoun *243*, 1938).

Much could be written concerning the general fiber connections of the hypothalamus with outside structures but an extensive discussion of the various contributions seems hardly worth while. It is generally agreed that the bulk of the afferent connections are primarily (or primitively) olfactory, reaching the hypothalamus through the medial forebrain bundle and the ansa peduncularis, besides the fornix and stria terminalis. Connections with the caudate and lentiform nuclei are frequently mentioned. Some authors postulate direct afferent connections from non-olfactory cortical areas. That some sort of cortical connection exists is strongly indicated by experimental work. However, von Milliser (*268*, 1932) could demonstrate no fibers passing from the neocortex to hypothalamus in the rat in studying degeneration from cortical lesions. Levin (*226*, 1936) could find no connection between frontal cortex and hypothalamus in the monkey. It is very likely that cortical influences are brought to bear upon the hypothalamus indirectly by way of the thalamus proper. Clarke and Boggon (*51*, 1933) and Walker (*384*, 1936) say that the dorso-medial nucleus of the thalamus sends fibers to the hypothalamus by way of the periventricular system; Laruelle (*219*, 1934) does not figure such connections. Roussy and Mosinger (*327*, 1934), Karplus (*188*, 1937) suggest the possibility of direct sensory paths to the hypothalamus.

Internuclear connections have been frequently mentioned, but little of certainty is known about them. The descending efferent connections are said to be with the mesencephalic tegmentum by way of the medial forebrain

bundle and other diffuse systems (fasciculus tuberis descendens of Nicolesco), to lower vegetative centers by way of the dorsal longitudinal bundle, and periventricular fibers into the central gray of the aqueduct. Beattie, Brow and Long (*18*, 1930) and Roussy and Mosinger (*326*, 1934) postulate descending connections in the medial longitudinal fasciculus. Efferent connections with thalamus and striatum have been suggested by Greving (*119*, 1931), Clark (*53*, 1936) and Roussy and Mosinger (*326*, 1934). For detailed descriptions of anatomical findings consult Greving (*119*, 1931), Huber and Crosby (*163*, 1930), Nicolesco and Nicolesco (*281*, 1929), Rioch (*322*, 1931), Krieg (*214*, 1932), Beattie (*20*, 1932), Laruelle (*219*, 1934), Roussy and Mosinger (*326*, 1934).

Some important information as to descending paths from the hypothalamus to lower effector mechanisms has been yielded by experiments in which stimulation of the hypothalamus has been carried out before and after partial sections at various levels of the brain stem and spinal cord. Thus Karplus and Kreidl (*191*, 1912) found that the pupillary dilatation produced by hypothalamic stimulation persisted after hemisection of the cervical cord, but was abolished by hemisection of both sides at different levels, and they postulated a crossing of the pathway in the cervical cord. Very recently, Magoun, Ranson and Hetherington (*249*, 1938) have performed extensive experiments along the same line after sections of varying extent at levels in the midbrain, pons and cervical spinal cord. In the midbrain, according to these workers, there are possibly some connections via the central gray, but reactions from the hypothalamus could still be obtained after destruction of the central gray, medial longitudinal fasciculus and the tegmentum adjacent to the central gray. These findings are at variance with those of Beattie, Brow and Long (*18*, 1930). The descending connections in the midbrain may thus be said to be widely and diffusely represented in the mesencephalic tegmentum. Similarly, in the pons, descending connections in the periventricular regions were found to be of a minor order, the bulk of the fibers extending into the lateral portions of the tegmentum. As for decussations, these workers found no evidence for crossing of the path for bladder contraction above the first cervical segment. The paths for respiratory and blood pressure responses, however, seemed to undergo partial crossing even above the midbrain levels studied. The pressor pathway is predominantly uncrossed as far caudalward as the first cervical segment, below which the degree of crossing appears to be greater.

It is also of interest to note that Langworthy and Richter (*218*, 1930) traced the paths for galvanic skin responses from forebrain and diencephalon by stimulation methods caudally through the brain stem in the pyramidal tracts and also in the lateral portion of the midbrain and pons—in the latter instance in the region of the rubrospinal tracts.

Studies of the Functions of the Hypothalamus

Besides clinico-pathological studies, several approaches to the investigation of the physiology of the hypothalamus have been used. One of these has been the study of animals after removal of higher portions of the brain; in another attempts have been made to arouse the hypothalamus or parts of the hypothalamus to abnormal activity under otherwise constant conditions by artificial means of stimulation, including the use of drugs, mechanical irritation

and electrical current. Still another approach has been the suppression of all or part of the hypothalamus in otherwise intact animals by the use of drugs or direct destruction. While the participation of the hypothalamic region in various visceral functions had been suspected for many years (see Cushing *64*, 1932), the first real evidence for such function was offered by the stimulation experiments of Karplus and Kreidl (*189–194*) begun in 1909. Let us then consider some of the work accomplished by this method.

The effects of direct stimulation of the hypothalamus: Karplus and Kreidl (1909) approached the hypothalamus in cats by exposing the brain freely and placing the animal upon its back so the brain dropped somewhat from the floor of the skull. Faradization behind the optic chiasm lateral to the infundibulum produced dilatation of the pupils and retraction of the nictitating membrane. Section of the cervical sympathetic trunks abolished this response. The reaction was still obtainable long after removal of the hemispheres and most of the basal ganglia, and since this largely removed the possibility of stimulating fibers of passage, the authors believed they had established a true center for autonomic reactions. Later work (1910, 1912) confirmed these results, and experiments in which hemisections of the cervical spinal cord were performed seemed to establish that the path ran from the diencephalic center of one side to the cervical sympathetic of both sides. They also suggested that the area in question may exert an inhibitory action on the oculomotor nucleus, since hypothalamic stimulation after cervical sympathectomy still elicited slight pupillary dilatation. Hypothalamic stimulation was further observed to call forth lacrymation, salivation, sweating from the pads of the feet and contraction of the full or empty bladder. Increases in blood pressure from such stimulation (1918) were found to occur in curarized animals. These rises were not obtained from the infundibulum (1927), but were obtained from the hypothalamus after removal of hypophysis or adrenals. The latter operations were also without effect on the sweating, etc. responses. The elicitation of such reactions by stimulation of afferent fibers in peripheral nerves led the authors to believe that the hypothalamus was sensitive to pain stimuli from the periphery and that it participated in pain reflexes. In 1930 and 1933, Karplus and Peczenik (*195* and *196*) reported that stimulation of the hypothalamus caused a change in the cerebrospinal fluid whereby the latter became capable of causing contraction in uterine strips and expansion of the melanophores of frog skin. This change, they believed, was traceable to a release of pituitrin into the cerebrospinal fluid, and was not dependent upon activity of the cervical sympathetic, general irritability or pain.

In 1912 Aschner (*6*) attempted to stimulate the hypothalamus by piqure, and with various electrical and chemical means, and reported glycosuria, elevation of blood pressure, and contraction of the bladder, as well as contraction of the uterus in pregnant dogs and cats. Stimulation of the hypophysis was without effect. Lichtenstern (*231*, 1912) observed contraction of the bladder upon stimulation of the hypothalamus; the response was abolished by section of the nervi erigentes, but was enhanced by removal of cerebral cortex. Leschke and Schneider (*224*, 1917), using the piqure method, found no changes in energy metabolism or in chloride or allantoin output after hypothalamic irritation. They did find slightly diminished nitrogen metabolism. The piqures made by these

workers often amounted to rather gross lesions. Schrottenbach (*339–342*, 1914, 1916), apparently inspired by the work of Karplus and Kreidl, studied patients and animals with diencephalic lesions for psychophysiological disturbances. He observed interference with psychic vasomotor, cardiac and pupillary changes in his patients, and alterations in the respiratory and vasomotor responses to various stimuli in rabbits, concluding that the hypothalamus area was important for mediating such effects. This, while not dealing with direct stimulation, was one of the earlier observations on the relation of the hypothalamus to homeostasis. In 1925, Houssay and Molinelli (*160*) observed increased secretion of adrenalin in response to stimulation of the infundibular portion of the third ventricle. Schurmeyer (*343*, 1926) observed melanophore expansion in frogs after hypothalamic puncture and ascribed it to release of hormone from the pars intermedia of the hypophysis. Wang and Richter (*388*, 1928) confirmed the general findings of Karplus and Kreidl, and while unable to observe sweating in their cats, they obtained good galvanic skin responses from the footpads. These were abolished by section of the sympathetic nerves to the limb. Wang, Pan and Lu (*387*, 1929) found the galvanic skin responses produced by stimulation of peripheral nerves were not greatly changed by removal of the hemispheres, but showed considerable diminution in intensity and prolongation of latent period after decerebration below the diencephalon. This finding, so different from the effects of decerebration on somatic motor reflexes, seemed to establish the importance of the hypothalamus for this type of reaction. That the latter is not absolutely essential, however, is shown by the fact that such responses may still be obtained in spinal animals. Langworthy and Richter (*218*, 1930) also obtained galvanic skin responses from stimulation of the hypothalamus and areas rostral to the latter. Their work upon the possible descending paths has already been described.

Lewy (*228*, 1928) stimulated the hypothalamic region electrically, specifically approaching, he says, the corpus subthalamicum (which is not really a part of the hypothalamus), and observed dilatation of the pupils, salivation, lacrymation, but little change in blood pressure. Shinosaki (*346*, 1929) also observed pupillary dilatation upon stimulation, and was quite emphatic in designating the subthalamic nucleus as the effective point. It is of interest that Lewy was among the first to use the Horsley-Clarke stereotaxic apparatus for stimulating the hypothalamus. This instrument (Horsley and Clarke *159*, 1908) is of great value in approaching the more remote parts of the brain with a minimum of damage to other portions. By its use, insulated needle electrodes may be inserted with considerable precision to desired places, and stimulation carried out with faradic or other types of current. Restricted localized lesions may also be produced electrically. Points stimulated or destroyed can afterward be identified in microscopic sections. Discussion of the uses of this technique has been given by Ranson (*310*, 1934). Using this method, Ingram, Ranson and Hannett (*173*, 1931) found that pupillary dilatation could be elicited from many points beside the subthalamic nucleus. Ranson and Magoun (*316*, 1933) found by similar methods that the dilatation was obtainable particularly from the lateral hypothalamic area and the region surrounding the fornix, the response first appearing at the anterior hypothalamic level. The descending pathways became quite diffuse in the midbrain. The finer localization possible in these

experiments indicated that the results of Lewy and Shinosaki were probably due to spread of current from the subthalamic nucleus to the adjacent lateral hypothalamic area. The stimulation of this region was also observed by Magoun and Ranson to produce acceleration of respiration frequently associated with running movements. From the rostral part of the hypothalamus typical "spitting" movements of the mouth and tongue associated with forceful expiration were obtained.

Before entering into further discussion of the work of Magoun, Ranson and their co-workers, it may be well to describe the investigations of Beattie and his group. Beattie, Brow and Long (*19*, 1930) working with cats observed that the cardiac arrhythmias produced by chloroform anesthesia and said to be due to abnormal sympathetic activity or discharge of adrenalin were abolished by lesions in the posterior but not by removal of the anterior part of the hypothalamus. Extrasystoles and elevation of blood pressure were also produced by electrical stimulation of the caudal part of the hypothalamus. These effects were considered to be in part due to release of adrenalin, but also occurred in the absence of the adrenal glands. Lesions of the posterior hypothalamus lengthened the auriculo-ventricular conduction time; stimulation shortened it. The study of efferent paths from the hypothalamus carried on by these authors has already been mentioned. It is of interest, that lesions of the posterior hypothalamus produced transient glycosuria and polydipsia, drowsiness, and fall of body temperature, and loss of pilo-erection. Since the effect of destruction of the posterior hypothalamus on chloroform arrythmias differed from that of removal of the anterior or supraoptic portion, Beattie (*20*, 1932) postulated two functionally distinct areas in the hypothalamus—an anterior parasympathetic and a posterior sympathetic. The latter was also considered to be under some degree of control by the former, while inhibitory and excitatory influences over the whole were exerted by cortex and thalamus, respectively. Beattie did not believe there was evidence for a series of discrete centers, but that the activity of one or the other complex was generalized along the line of "mass reactions". Beattie (*21*, 1932) and Beattie and Sheehan (*22*, 1934) reported that stimulation of the lateral margin of the infundibulum (apparently included in Beattie's anterior area) produced increased motility and secretion of the stomach, with prolonged stimulation causing the appearance of patches of hyperaemia in the mucous membrane. Cutting the vagi prevented these effects. Increased tone of the bladder and slowing of the heart were also observed. On the other hand, stimulation of the posterior or sympathetic area resulted in obliteration of all gastric activity. There is some question whether the increased intragastric pressure observed by Beattie may not have been due to contraction of the abdominal muscles or to respiratory movements. Beattie and Kerr (*23*, 1936) added further support to the idea of segregation of function in the hypothalamus by reporting relaxation of the urinary bladder after stimulation of the posterior hypothalamus, with contraction resulting from stimulation of the anterior portion.

Other workers have reported results at variance with certain of Beattie's findings or interpretations, especially in regard to the existence of hypothalamic parasympathetic centers. The most detailed and painstaking investigations yet made of the hypothalamus by the stimulation method are those of Ranson, Magoun and Kabat. Using the

Horsley-Clarke technique these investigators have explored the hypothalamus and adjacent areas millimeter by millimeter, recording responses and correlating them with the exact points stimulated as determined histologically. The results of this work (Ranson, Kabat and Magoun, *315*, 1935; Kabat, Magoun and Ranson, *183*, 1935, *184*, 1936; Kabat, *181*, 1936) have been summarized by Ranson (*311*, 1934; *312*, 1936), and have been in general confirmed by Crouch and Elliott (*62*, 1936). Stimulation of the hypothalamus proper, and more specifically, the full extent of the lateral and the posterior areas, produced largely reactions of a sympathetic nature—elevation of blood pressure (accompanied, however, by little change in heart rate) and dilatation of the pupils. These responses were also obtained in curarized animals. Associated with them in ordinary anesthetized cats there was usually augmentation of respiration. Contraction of the bladder was obtainable from various points in the hypothalamus, but the authors were able to trace this response forward beyond the limits of the hypothalamus into the preoptic area and septum and suggested that when such reactions were elicited from the hypothalamus they were due to activation of descending pathways passing through it. Such other parasympathetic activities as could be aroused were also obtained from anterior areas. These responses, including depression of blood pressure, slowing of respiration, but rarely slowing of the heart or pupillary constriction, were effected from "the gray matter around the anterior commissure and near the ventral tip of the lateral ventricle and parts of the septum and preoptic area". The depressor response may well be due to stimulation of a cortical pathway, since it was traced forward into the frontal lobe. The authors admit the possibility of a parasympathetic center in the region mentioned, but question the existence of a general center of this sort, pointing to the fact that slowing of the heart and constriction of the pupils are rarely, and defecation, erection, salivation, lacrymation, and intestinal motility never obtained from this area in their experience. It was of interest that true hypothalamic stimulation producing hypertension and augmented respiration would, if maintained, spread to somatic motor centers, with running movements, struggling and clawing appearing. Even in anesthetized animals the total response thus produced resembled the effects of intense emotion. Results obtained on unanesthetized cats thus become of interest (Kabat, Anson, Magoun and Ranson, *182*, 1935). In these experiments various points in the interior of the brain were stimulated with needle electrodes oriented with the stereotaxic instrument and anchored firmly in the skull. With the electrodes in the lateral hypothalamic area a picture of intense emotional reactivity was produced, with pupil dilatation, erection of hair, violent struggling and clawing, acceleration of respiration and spitting. Fluoroscopic examination of gastro-intestinal movements showed that all movement ceased abruptly upon the onset of stimulation in this region; furthermore, stimulation in the possibly parasympathetic areas situated farther rostrally failed to induce any increased activity of the gut. It was pointed out by the authors that, by stimulation methods, the changes observed by Cannon (*48*, 1929) in excited cats or those appearing in cats lacking the inhibitory influences of the cerebral cortex (Bard *10*, 1928), could be reproduced. Mention of these factors in behavior will be made later. The pathways involved in facial and vocal components of emotional expression

have also been studied in cats and monkeys by Magoun, Atlas, Ingersoll and Ranson (*245*, 1937).

Direct confirmation of the findings of Houssay and Molinelli (*160*, 1925) that hypothalamic stimulation causes outpouring of adrenin, with the additional finding of release of sympathin into the circulation has been brought forth by Magoun, Ranson and Hetherington (*248*, 1937). Differential methods showed that both of these hormones are produced, but the authors were careful to show that direct nervous effects of stimulation are primary, in view of the prolonged latent periods of responses involved by such substances. That they may play a part in augmenting and prolonging hypothalamic influences was suggested as a possibility, and it was "concluded that the rôle of the hypothalamus in visceral innervation and emotional excitement is effected both by direct nervous influences and by humoral substances for whose release these nervous influences have been responsible".

Oddly enough, all these effects have been obtained from the lateral hypothalamic area, which includes mostly fibers of the medial forebrain bundle and relatively few nerve cells except in its caudal part. The medial portion, which contains the cell groups to which so much attention has been given by anatomists was relatively silent except for the caudal portion of the posterior hypothalamic nucleus—and responses obtained in the latter may be due to activation of decussating fibers. The reasons for this are obscure, since many of the fibers in the lateral areas must come from the hypothalamic cell groups, and few of the responses can be traced rostral to the hypothalamus proper. Perhaps the threshold of the axons is lower than that of the cells, or the concentration of fibers into a small area makes the activation of a larger number of nervous elements a possibility.

So much space has been devoted to the foregoing researches because of their basic importance and, in certain cases, because they represent such detailed, thorough-going and far-reaching investigations. Other important work must also be mentioned, but briefly. The work of Hess upon the effects of stimulation upon sleep will be discussed later. His work, of interest because of the employment of direct, pulsating current as means of stimulation also includes observations (*149*, 1935) on autonomic effects somewhat different in their localization from those of Ranson, Magoun et al. Van Bogaert (*376*, 1935) and Jaegher and van Bogaert (*178*, 1935) have also observed blood pressure elevations and acceleration of heart rate (if vagus is cut). The blood pressure response was abolished by sympathectomy or ergotamine administration. Van Bogaert also observed clonic and tonic convulsions. The latter were observed by Kabat, Anson, Magoun and Ranson only when strong stimuli were used. It is of interest that Morgan and Johnson (*279*, 1930) observed epileptiform convulsions during a period of a few hours following injection of dilute solutions of mercuric chloride into the hypothalamic region. Ectors, Brookens and Gerard (*82*, 1938) stimulated the exposed surface of the third ventricle wall and observed the usual responses. However, they believed that several distinct centers arranged anteroposteriorly could be designated, but since their anatomical localizations were macroscopic, direct correlation with specific cell groups was not possible. The rostral region gave responses suggestive of rage, the posterior of fear and pain. These centers were thought to be in the gray of the ventricle walls, with the pathways possibly in the

lateral region. Somatic responses were obtained from the posterior hypothalamus—some of them resembling the so-called tegmental response (Ingram, Ranson, Hannett, Zeiss and Terwilliger, *174*, 1932). Responses in which automatic and somatic effectors cooperate led the workers to suggest for the hypothalamus a rôle in the control of certain "discriminate" activities, presumably of an emotional character. However, these somatic responses were obtained from areas not far removed from the motor centers of the midbrain. Effects were apparently obtained from the gray substance and not from the lateral region, since the reactions were not observed when the electrodes were plunged a short distance into the wall of the ventricle. The possibility of stimulating fibers of the periventricular system must be considered.

Penfield and Stavraky (*293*, 1935), Stavraky (*359*, 1936), have demonstrated a relationship between the hypothalamus and vasomotor activity in the meninges in cats. They observed dilatation of pial arteries from stimulation of a circumscribed area in the ventral portion of the tuber cinereum and from a more diffuse area in the dorsal thalamus. Somewhat variable results were obtained in regard to constriction of these vessels, but stimulation between the cerebral peduncle and third ventricle produced such effects. The results were independent of blood pressure changes, and were not abolished by adrenalectomy, hypophysectomy or artificial respiration.

Very recently, Massermann and Haertig (*262*, 1938) have reported results tending to show the existence of parasympathetic elements in the hypothalamus. Using the stereotaxic apparatus, these workers found that movements of the gut could be produced in cats by weak stimuli applied to the anterior hypothalamic area, to the dorsal part of the supramammillary decussation and the mammillary bodies. Similarly weak stimulation of the suprachiasmatic region or of the ventral part of the supramammillary decussation caused inhibition of intestinal motility. With stronger stimuli the results of Kabat, Anson, Magoun and Ranson were confirmed. Also, small amounts of strychnine injected into the hypothalamus sometimes caused slight accentuation of intestinal movements; larger amounts produced spasticity and blanching of the gut. These findings, if confirmed, will support those who have suggested the presence of parasympathetic as well as sympathetic centers in the hypothalamus, the former apparently having the lowest threshold to electrical stimulation and effects so weak as to be readily masked or obliterated when the stronger discharges from the sympathetic elements are brought into play.

Other important evidence relating the hypothalamus to the autonomic nervous system has been presented by Bronk, Lewy and Larrabee (*37*, 1936) from the standpoint of electro-physiology. Action currents, led off the lateral hypothalamic area, were synchronous with the rhythmically occurring waves observed in efferent sympathetic nerves. Electrical stimulation of this area initiated corresponding volleys in such nerves. Furthermore, stimulating afferent nerves which ordinarily influence the efferent rhythms produced rhythmic changes in potential in the hypothalamus. It is also of interest that section of the brain stem rostral to the hypothalamus caused increased sympathetic discharge, while section caudal to the hypothalamus reduced the amount of rhythmic activity in efferent nerves without completely abolishing it.

Very recently Grinker (*120*, 1938) has developed a technique for electrical

stimulation of the hypothalamus in man. This is carried out through the sphenoid bone and has produced the sort of results found in animals, including marked elevations of blood pressure. Strong currents produce convulsive movements and changes in respiration and circulation. Therapeutic utilization of this method in schizophrenia is suggested. In cats this technique has been used in studying electrohypothalamograms, and it has moreover been observed that hypothalamic stimulation produces changes of an excitatory character in cortical action currents. Thus in some way the hypothalamus may affect cortical activity, if not by direct then by indirect connections, and possibly through hormonal or humoral influences.

A word should be added concerning the type of electrical current used in stimulation experiments. Most investigators have found ordinary faradic current satisfactory. Hess, (*147*, 1932), however, recommends a damped pulsating direct current as being most suitable for the activation of high-threshold vegetative elements without spread to somatic fibers. On the other hand, Harrison, Magoun and Ranson (*133*, 1938) have recently studied the thresholds to stimulation with various types of current in the brain stem, and found no advantage of the use of direct, damped current pulses over ordinary faradic shocks. It was found that the latter could be controlled sufficiently for limited localization of stimulating effects. The use of direct current is likely to involve polarization of electrodes and, even more serious, electrolytic destruction of brain tissue.

It is necessary, further, to consider work in which means other than electrical have been used to excite or depress the supposed centers of the hypothalamus. It will not be possible to review all the work relating to the action of drugs and chemicals but some of the more important may be mentioned. It should be pointed out in the first place that the Germans have long considered that narcotic drugs of the barbiturate type act on the diencephalon (Keeser and Keeser, *198*, 1927, Sahlgren, *333*, 1934). The fact that the intraventricular injection of ergotamine was observed by Hess (*148*, 1932) to induce sleep led him to postulate a suppression of the sympathetic system by such means. Demole (*70*, *71*, 1927) observed the injection of small amounts of $CaCl_2$ into the tuber to cause parasympathetic manifestations and sleep, while KCl produced reactions of a sympathetic type. Injection of these substances elsewhere in the brain did not cause these effects. These results have been supported by Lafora (*217*, 1931), Marinesco, Sager and Kreindler (*257*, 1929) and contradicted by van Bogaert (*376*, 1935). Hasama (*135*, *136* 1930) reported that direct injection of K, Ba and Na salts into the tuber cause elevation in temperature and sweat secretion in cats, while Mg and Ca were inhibitory to these effects. That the positive results were of sympathetic nature was indicated by the fact that they were abolished by ergotamine. Colucci and Penta (*58*, 1932) observed that injection of ephedrine into the third ventricle produced sympathetic effects more marked than those obtained by subcutaneous injection. Leschke (*222*, 1920) says that death results from application of 1:1000 adrenin to hypothalamus. Karplus (*188*, 1937) denies this, and Spiegel and Saito (*355*, 1924) found no effect from it. The latter observed that posterior pituitary extracts injected into the third ventricle lowered blood pressure.

The site of action of various hormonal substances, and their effect on the hypothalamic structures is of great interest. Raab (*307*, 1926; *308*, 1930;

309, 1934) studying the effect of pituitrin and his hypophyseal extract "Lipoitrin" in lowering blood fat, reported that results were much more marked when these substances were injected into the third ventricle, and that they were no longer obtainable with other methods of administration when the hypothalamus was destroyed or sympathectomy performed. Cushing (*63*, *64* 1932), carried out a long series of experiments on the intraventricular injection of drugs in patients with striking results. Pituitrin produced marked parasympathetic effects—flushing, sweating, vomiting, etc. with fall in body temperature and basal metabolic rate, but little if any change in blood pressure. These were decidedly different from effects produced by subcutaneous or intravenous administration. Pilocarpine gave similar results. Patients with hypothalamic involvement due to tumors failed to react, and the effects mentioned could be prevented by giving atropin or avertin. Similar effects, with more marked fall in blood pressure, but with slight fall in body temperature were noted by Light and Bysshe (*234*, 1933). In rabbits (Light, Bishop and Kendall *233*, 1933) pilocarpine given intraventricularly induced a mixture of sympathetic and parasympathetic responses. Although Cushing was unable to demonstrate an antipyretic effect of pituitrin in lower animals, he postulated a possible parasympathetic center concerned in such a function in the walls of the third ventricle. Bouckaert (*28*, 1934) observed that the injection of posterior lobe extract into the cerebrospinal fluid produced elevation of blood pressure everywhere in the body except in a denervated limb, postulating a central pressor action for the drug.

Dikshit (*73*, 1934) found cardiac irregularities appeared following injection of acetylcholine into the lateral and third ventricle. Large doses produced arrest of respiration. Either a rise or fall in blood pressure was noted. The effect was believed to be upon the hypothalamus. The application of acetylcholine directly to the cut surface of the brain elicited no effects. It is also of interest that intraventricular administration of 0.1 to 0.5 gamma of acetylcholine produced a sleep-like state. Pilocarpine, on the other hand, caused excitation. Henderson and Wilson (*144*, 1936) injected acetylcholine into the lateral ventricle in man, noting vomiting, defecation, urination, sweating, with no change in blood pressure, but slight slowing of the heart, and little change in temperature. In some cases there was a tendency to sleep. The doses required were less than the intravenous dose. Eserine produced similar effects, and in view of the known protective action of this substance against the cholinesterase the author suggested they were due to accumulation of naturally occurring acetylcholine in the brain. Atropine counteracted the influences of these drugs. The effect must be central for in one case sweating did not occur in a limb which had been sympathectomized, but the authors remarked that these cholinergic effects were not necessarily due to stimulation of a center in the upper part of the brain. Silver and Morton (*347*, 1936) injected 2 to 4 gamma of acetylcholine directly into the hypothalamic region in cats, observing a small rise in blood pressure followed by a sharp fall of 20 to 50 mm. of Hg lasting 1 to 2 minutes. Injection in the lateral ventricle gave similar but less consistent results, and in unanesthetized cats caused drowsiness. The reactions to acetylcholine thus far described have been largely parasympathetic. Suh, Wang, and Lim (*364*, 1936), however, injected acetylcholine intracisternally or applied it directly to the floor of the

fourth ventricle, observing elevation of blood pressure and augmentation of respiration due, according to these workers, to stimulation of an area in the region of the vestibular nuclei. The question arises whether localized centers should be hypothecated on the basis of intraventricular injection. The localization of effects in the hypothalamus from injection in the lateral ventricles is justified by certain workers on the basis of the time of appearance of responses compared with the time required for perfusion or circulation to lower centers. The difference in acetylcholine effects when administered intracisternally from those obtained by injection in the upper ventricle perhaps justifies this view. The question is made difficult, however, by the finding of Lafora that substances injected into the fourth ventricle passed quickly into the third ventricle (vide also Hamperl and Heller *130*, 1933). The matter of suitable dosages has received relatively little attention. In the opinion of the present writer, however, these methods do not justify too closely drawn conclusions, especially when more direct and accurate methods of study are available.

Nevertheless, the evidence cited here has led the various authors to the conclusion that autonomic centers do exist in the hypothalamus. We must now consider some interesting work which led its authors to different conclusions. Van Bogaert and his co-workers (*377*, 1936) confirmed the usual findings as to electrical stimulation, using changes in arterial tension as criteria. However, he believed that chemical means of stimulation (chiefly direct application of concentrated ammonia) offered better localization. From a retro-hypophyseal area he obtained vasoconstriction, adrenin discharge causing hyperglycemia, fall in fatty acids of the blood and very slight elevation of blood calcium with concomitant lowering of blood potassium. Finding some intermingling of type responses, he could distinguish no specifically parasympathetic or orthosympathetic centers in this region. Surprisingly, in view of the work of Ranson, Kabat and Magoun, he found a depressor area in the lateral hypothalamus, the depression obtained here not being affected by vagotomy or atropine. In view of the latter fact, he suggests that there is no real vasodepressive path, but that this area merely suppresses the tone of bulbar depressor centers. Van Bogaert argues against the idea of regulatory centers in the hypothalamus for the following reasons: 1) very strong stimuli are required to give pressor effects; 2) the lack of specificity of stimuli because, a) adrenin injection in the hypothalamus had no effect on blood pressure, b) posterior lobe extract also had no effect, c) suboccipital injection of these substances does have effects which are not altered by removal of the hypothalamus, d) strong Ca and K solutions, ordinarily antagonistic, produce hypertonia only, with no depressor effect. He concludes that since the hypothalamus is insensitive to the effects of the hypophyseal hormones (in his opinion), and to specific chemical excitants of the para- and orthosympathetic systems, it does not contain cardio- and vaso-regulatory centers, but is only a place of passage for vegetative paths which probably come from higher levels. The effects themselves are mediated by bulbar centers, the tone of which is subject to augmentation or inhibition from above.

The suggestions of van Bogaert meet with serious opposition in the findings of Rioch and Brenner (*323*, 1938), who found that stimulation of the posterior hypothalamus in chronically decorticated cats gave results similar to those observed by Ranson and his co-workers.

These stimulations were carried out after sufficient time had elapsed for degeneration of fibers from the cortex. Inhibition of respirations and slowing of the heart, however, were not observed, which indicates that such responses may be due to stimulation of cortical efferent pathways. No parasympathetic center was demonstrated. Magoun (*243*, 1938) has reported almost identical findings in cats after removal of the frontal lobes, allowing several weeks for degeneration of corticifugal fibers. Here, also, only the vasodepressor and respiratory inhibitory effects were depressed.

The work thus far cited constitutes evidence of two sorts for or against the hypothesis of hypothalamic autonomic regulatory centers. Other methods of investigation of the problem and the possible relation of the hypothalamus to certain specific functions remain to be considered.

The relation of the hypothalamus to peptic ulcer of the neurogenic type should be briefly discussed. Cushing (*65*, 1932) opened this question when he reported the occurrence of acute, perforating lesions of the esophagus, stomach and duodenum after operation for cerebellar tumor in three cases. He gives a good summary of previous work on the etiology of peptic ulcers, especially of neural factors involved, and postulated in such cases irritative interference with fiber tracts from a parasympathetic center in the hypothalamus to the vagal center, or paralysis of sympathetic fibers with vagal release. Numerous similar cases have been since described in the literature. Light, Bishop and Kendall (*232*, 1932) reported the production of gastric lesions in rabbits by the injection of pilocarpine into the cerebrospinal fluid. Fortunately, perforating lesions did not apparently follow Cushing's intraventricular injection experiments. Watts and Fulton (*391*, 1935) found erosions and ulcerations of the gastric mucosa after producing extensive lesions in the hypothalamus in monkeys. Hoff and Sheehan (*154*, 1935) reported similar results from lesions in the tuber region opening into the third ventricle, also in monkeys. Identical lesions, however, were not always associated with gastric lesions. Keller (*201*, *202*, 1936) and Keller and D'Amour (*203*, 1936) observed lesions of the stomach mucosa in dogs with hypothalamic lesions. Bilateral vagotomy in such animals prevented the appearance of craters, but hemorrhagic states occurred. On the other hand, abdominal sympathectomy prevented hemorrhages but did not keep craters from forming. Keller suggests that these results may have been due to direct traumatic effects of the lesions or else to more remote irritation due to contamination of the cerebrospinal fluid with debris from the lesions. It is perhaps noteworthy that Keller's animals were kept under varying environmental conditions. Martin and Schnedorf (*259*, 1938) have recently criticized the foregoing work and have studied the effects of a wide range of hypothalamic lesions in numerous cats and monkeys, but found no postoperative changes in gastric motility or secretion and no signs of ulceration or erosion. The writer has found no significant evidence of gastro-intestinal lesions in some hundreds of animals with hypothalamic lesions. The reason for variations in results is not yet clear.

The hypothalamus, temperature regulation and energy metabolism: It will not be possible to cover all the literature regarding the central neural regulation of the body temperature. In the older works, the participation of higher neural mechanisms was known and functions allocated to the diencephalon and corpus striatum (Ott *283*, 1891, Aronsohn and Sachs *5*, 1884). Although

clinically it has been shown that patients with cervical spinal cord transsections may recover a degree of temperature control, and although cases with diencephalic injury have been reported without temperature disturbances the idea of a higher regulatory mechanism still persists. The participation of the autonomic system in this function is shown by the fact that sympathectomized animals are somewhat deficient in heat control (Sawyer and Schlossberg *336*, 1933), but in these animals somatic heat regulatory mechanisms (shivering and panting) persist.

Barbour (*9*, 1912) demonstrated shifts in body temperature upon warming and cooling the brain, but did not attain very definite localization, believing the crucial point to be the caudate nucleus. Isenschmid and Krehl (*175*, 1912) observed that removal of the forebrain and diencephalon caused complete loss of heat regulation in rabbits. Leschke (*220*, 1913) produced poikilothermic rabbits by stab wounds in the hypothalamus, and Isenschmid and Schnitzler (*177*, 1914) on the basis of experimental lesions located a regulatory center in the caudal part of the hypothalamus near the ventral surface, extending laterally about 3 mm.—a degree of localization which has hardly been excelled by more recent methods. The hyperthermia produced by irritative lesions (Wärmestich) of the hypothalamus was linked with the autonomic nervous system by Freund (*96*, 1913) who found such effects abolished by vagotomy and cervical cord section. The work of Barbour was confirmed by Prince and Hahn (*306*, 1918), who showed that peripheral vasoconstriction and vasodilatation were connected with the regulatory mechanism. Sachs and Green (*331*, 1917), Moore (*275*, 1918) and Kornblum (*212*, 1925), on the other hand, did not confirm the existence of heat centers in the brain. The incapacity of decerebrate animals to maintain normal body temperature at room temperature has been discussed by Bazett and Penfield (*15*, 1922) and Bazett (*16*, 1932). Bazett, Alpers and Erb (*17*, 1933) studied cats after transections of the brain stem and observed that if the caudal part of the hypothalamus was left intact, ability to maintain normal temperature was regained after a few days. The anterior portion of the hypothalamus was necessary, however, for adjustment to high environmental temperatures.

Frazier, Alpers and Lewy (*95*, 1936), placing lesions in various parts of the hypothalamus, localized the heat regulatory center in the region of the anterior hypothalamic nuclei, but they presented only a few cases which did not survive long. Teague and Ranson (*367*, 1936), on the other hand, showed that cats with lesions in the rostral portion maintain normal temperatures ordinarily but do not when the environmental temperature is raised. These workers suggest the existence of two centers, one for adjustment to high temperatures and one for low (cf. Bazett, Alpers and Erb *17*, 1933). After producing bilateral hypothalamic lesions, Ranson, Fisher and Ingram (*314*, 1937) observed transient hyperthermia or prolonged hypothermia; the latter occurred if the lesion involved the lateral hypothalamic areas at the level of the mammillary bodies. The hypothermia usually disappeared after some weeks, but even though such monkeys maintained normal temperatures under ordinary conditions, they could not react normally to unusually high or low room temperatures. Except for their relative lateral position, the lesions in these animals conformed closely as to level with those described in a hypothermic human case by Alpers (*2*, 1935). The findings of Teague and Ranson and the idea of a double center

were thus supported. Since the caudally placed lesions produced loss of ability to compensate for high as well as low temperatures interruption of descending pathways was presumed.

As has been intimated, some authorities do not agree that removal of the hypothalamus permanently abolishes temperature regulation, but hold that other centers for such function exist. Dworkin (*79*, 1930) observed shivering in rabbits after transsection through the medulla, with slight elevations of temperature. Hasama (*135*, 1930) believes a subordinate center lies in the region of the dorsal vagus nucleus in the medulla. Glaubach and Pick (*112*, 1933) agree that midbrain rabbits have no temperature control; however, after transsection caudal to the colliculi their animals regained normal or showed high temperatures. They suggest two centers—one in the hypothalamus the loss of which causes low body temperatures, and one in the midbrain, the loss of which causes high temperatures. Keller (*200*, 1933) and Keller and Hare (*205*, 1932) reported that midbrain cats may regain a measure of temperature control in time, but that pontine preparations (transsection at rostral border of pons) have no control at all. The midbrain preparations reacted to high room temperatures (panting) but not to low. Such experiments, together with a study of effects of hypothalamic lesions led Keller to hypothecate a mechanism in the dorsal part of the hypothalamus concerned in heat production, and another in the midbrain related to heat loss. This conception hardly fits with that of Ranson and his co-workers. Thauer (*370*, 1935) is an outstanding opponent of the concept of a heat regulatory center the loss of which is irreparable. He maintains that while rabbits become "thermolabile" for a few days after cervical spinal cord section, they soon regain normal control even under extreme conditions. This replacement mechanism he believes to be a peripheral one. More recently, Thauer and Peters (*369*, 1937) report that the hypothermia and thermolability resulting from removal of the hypothalamus in rabbits is transient; after 10 to 14 days such an animal can maintain a normal temperature. Spontaneous fever was observed in two such rabbits, and in one injection of Pyriferin induced artificial fever. It is difficult to reconcile all these findings, many of which are diametrically opposed. Confirmation of Thauer's work in the same and different species is needed, with more work on temperature control mechanisms below the diencephalon. The evidence for a heat regulatory mechanism of the highest importance in the hypothalamus is, however, quite generally accepted. Unfortunately its exact localization is not known, at least in terms of cell groups. A fair degree of general spatial localization has been worked out by Isenschmid, Ranson and others.

The mode of activation of the heat control apparatus is generally held to be change in the temperature of the circulating blood. By its position the hypothalamus is well shielded from the influence of external temperature changes. Serota and Gerard (*345*, 1938) find the temperature of the superficial parts of the brain lower than that of the deep. Various experiments on the effects of heating and cooling the brain have been mentioned. According to Hasama (*134*, 1929) temperature changes on heating and cooling the hypothalamus itself were obtained by more precise means than those of Barbour. Duschko, Faitelberg, Gugel-Morosowa and Ssinelnikow (*77*, 1934) produced similar effects by changing the temperature of the carotid blood. The most precise and carefully controlled work thus far is that of Magoun,

Harrison, Brobeck and Ranson (*247*, 1938). With low voltage, high frequency current passing between electrodes oriented with the Horsley-Clarke stereotaxic apparatus heating of localized areas in the hypothalamus was carried out. The areas which responded by producing accelerated respiration, panting and even sweating lay in the medio-caudal part of the ventral telencephalon and could be traced back through the dorsal part of the hypothalamus and the ventral thalamus. At the upper end of the mesencephalon they were located near the central gray of the aqueduct. This precise determination of the location of structures which presumably are activated by elevated blood temperature is well correlated with earlier findings of Teague and Ranson and Ranson, Fisher and Ingram. Whether the caudal extent of this area is a conduction path or contains reactive cells is not known. However, the finding by Lilienthal and Otenasek (*235*, 1937) of an essential area for panting in the caudodorsal portion of the diencephalon might indicate the presence of reactive self-sufficient elements there.

Mention of panting necessitates brief discussion of effector factors in heat control. Pinkston, Bard and Rioch (*304*, 1934) noted alteration in the type of panting after removal of much of the forebrain. Hammouda (*129*, 1933) observed that panting occurs only when the diencephalon remains intact. The work of Lilienthal and Otenasek and Magoun et al., has just been mentioned. Keller (*200*, 1933) alone has reported the persistence of panting after removal of areas above the midbrain. Peripheral vasodilatation has already been mentioned (Prince and Hahn); more work on this mechanism in its relation to central control is needed. Sweating has been repeatedly observed after hypothalamic stimulation (Karplus and Kreidl, Wang and Richter, Langworthy and Richter, et al.). Hasama (*134*, 1929), using electrical, mechanical and thermal stimulation, mapped a sweat secretion zone in the cat extending from the mammillary bodies upward to 4 mm. rostral of the chiasm, and from the midline 4 mm. lateral. Warm stimuli produced profuse sweating, cold stimuli, slight sweating. The effect of the former was abolished with atropine, of the latter with ergotamine. He postulated therefore two sorts of sweat secretion, aroused a) by a parasympathetic mechanism activated by warm stimuli; and b) by a sympathetic mechanism activated by cold stimuli. He also observed that shifts to the acid side of the pH of fluid bathing the hypothalamus stimulated sweat secretion.

Some of the work on the effects of drugs and toxins must be mentioned, although no real attempt at a discussion of the sites of action of pyretic and antipyretic substances will be made. Freund and Strasmann (*97*, 1912) reported that no experimental fever could be produced after cervical cord transsection. Isenschmid (*176*, 1913) observed that Antipyrine had no effect in rabbits deprived of heat control mechanism, whereas sodium salicylate, quinine and morphine produced temperature changes by peripheral action. Hashimoto (*137*, *138*, 1915) reported that the increased temperature following intracerebral administration of horse serum in sensitized rabbits does not appear after destruction of the heat center. B-tetrahydronaphthylamine also had no effect in such rabbits. Direct heating or cooling the brain by Barbour's method had no effect upon artificial fevers produced by the latter, adrenin or ephedrine. The opposite is true in fevers caused by typhus bacilli or in anaphylactic fevers. The antipyretic action of Antipyrine and sodium

salicylate was reinforced by warm stimuli, opposed by cold. An interesting suggestion resulted from heating and cooling opposite sides of the brain simultaneously. It seemed the reaction of the body temperature took place only according to the type of stimuli applied on the left side. Hashimoto therefore made the suggestion, which has not been well received, that the left side was dominant. Solari (*352*, 1931) found the pyretic effects of B-tetrahydronaphthylamine and colon bacilli persisted after tuber lesions in dogs. Kym (*216*, 1934) on the other hand claims that the occurrence of fevers produced by such substances is hindered by injection of $CaCl_2$ solution into the hypothalamus. Pinkston (*303*, 1935) noted delay in the febrile reaction to typhoid-paratyphoid vaccine in sympathectomized cats. Ranson, Jr. (*313*, 1938) studied carefully the effect of intravenous injection of typhoid-paratyphoid vaccine in cats, and noted a cyclic effect in which there was a rise in temperature followed by a fall through three successive peaks. During the rise, the activation of the heat production and retention mechanisms was accompanied by sympathetic signs; during the fall, with heat loss, there were parasympathetic signs. Under abnormal conditions, as anesthesia, the heat loss mechanism only may be activated, with resulting fall in temperature and signs of parasympathetic activity. The same is said to be true in cats with certain hypothalamic lesions, but full details are not yet available. These findings should be compared with those of Hasama regarding the sweating mechanism. Such a dissociation of mechanisms for heating and cooling fits in well with the findings of Ranson and his associates. Morgan (*277*, 1938) reports finding chromatolysis in the tubero-mammillary, paraventricular and supraoptic nuclei after experimental fever produced by injection of typhoid or bronchisepticus toxin.

Raab (*307*, 1926) has suggested an analogy between the nervous control of chemical heat regulation and that of fat metabolism, since in his experience "wärmestich" caused a fall in blood fat similar to that caused by pituitrin (*cf.* van Bogaert *376*, 1935). The effect of pituitrin in lowering blood fat, according to Raab, depends upon the integrity of the tuber cinereum. Injection of antipyretics abolished this reaction to pituitrin. Such experiments, linking temperature control to fat metabolism have not been confirmed by other workers so far as the present writer knows.

Little research has been done with reference to any relation between the hypothalamus and the general energy metabolism, and no really systematic studies have been carried out so far as the effects of lesions or stimulation are concerned. Cushing (*63*, *64*, 1932) observed lowered basal metabolic rates in patients receiving pituitrin intraventricularly. Grafe and Grünthal (*114*, 1929) reported falls in B.M.R. of 20–36 per cent after injection of silver nitrate into the hypothalamus (unilateral lesions) in dogs. Occasional adiposity was observed. Andreu-Urra (*4*, 1932) observed diminished B.M.R. in 16 of 22 dogs receiving similar treatment, and suggested a close relationship between the cell groups controlling temperature and basal metabolism. Mazzoco (*264*, 1932) found the B.M.R. of dogs with tuber lesions to be about 15 per cent lower than normal; this was not quite as low as that of hypophysectomized dogs. Bruhn (*33*, 1934) reported one monkey in which the B.M.R. was lowered about 12 per cent after a lesion had been produced in the hypothalamus. The close anatomical and possibly functional rela-

tionship between hypothalamus and hypophysis is a handicap in performing such experiments. For example, in the matter of causes of certain types of adiposity it has not yet been determined whether dysfunction of one or the other exists—or if it is dysfunction of both. Clinically, evidence can be cited to prove either side of the argument. Smith (*350*, 1930), who produced enormous adiposity in rats by injection of chromic acid into the sella turcica, was inclined to place the blame upon the hypothalamus rather than the hypophysis, but no anatomical findings were presented. Camus and Roussy (*45*, 1922), Bailey and Bremer (*8*, 1921), and others have reported adiposity in dogs with tuber lesions. On the other hand, Ranson, Ingram and associates have observed no adiposity in some hundreds of cats with various sorts of hypothalamic lesions, and only one monkey out of forty-odd became obese. The lesions in this case were no different than those of other monkeys. This animal, surprisingly, matured sexually very suddenly and possibly precociously, and the normality of the anterior lobe of the hypophysis could not be ascertained with certainty. The whole question of the hypothalamic-hypophyseal system and adiposity remains open for further study.

A possible relationship between the hypothalamus and the thyroid, which naturally implies metabolic function, has been suggested by Fenz (*86*, 1937) who reported that barbituric acid derivatives, which are supposed by some to act by way of the hypothalamus, are of therapeutic value in treating cases of exophthalmic goiter, reducing the B.M.R., slowing the pulse, increasing insulin sensitivity and modifying the psychic manifestations, in some instances permanently. Since there appeared to be a fall in blood iodine upon such treatment, a depression of thyroxin production by suppression of a thyroid secretion center in the diencephalon was suggested. It was also proposed that the action of produced thyroxin was depressed by similar suppression of diencephalic centers through which it has part of its action. Hoff, Gentzen and Klemm (*157*, 1937) confirmed such an action of these drugs in certain thyrotoxicoses but found the effect a transient one. They found Prominal administration in animals to have no effect upon the histological structure of the thyroid although it caused the elevated B.M.R. of guinea pigs receiving thyroxin or thyrotropic hormone to fall sharply. Furthermore, it did not prevent the histological change in the thyroid due to activation of the latter by thyrotropic hormone. They believe, therefore, that while thyroxin undoubtedly acts directly upon a tissue substrate, it also produces part of its effects via an autonomic metabolism center. It is upon the latter that the Prominal acts. In Basedow's disease this center may be hyperirritable, along with the one controlling the production of thyrotropic hormone by the hypophysis. More experimental work along these interesting lines is needed.

The hypothalamus and water and mineral metabolism: The question of the participation of the hypothalamus in the control of water balance brings in a dual consideration, for the hypophysis is also undoubtedly related to this mechanism. We have, therefore, for consideration a perfect example of diencephalo-hypophyseal activity, in which also we will find the only well established localization of a function in a specific cell group. The clinical syndrome of diabetes insipidus first directed attention to this matter and much of our information has come from the clinical and experimental study of this condition. The literature on dia-

betes insipidus has been reviewed by Leschke (*221*, *223*, 1919, 1933) Meyer (*266*, 1926), Staemmler (*358*, 1932) and recently a large amount of the work has been reviewed analytically by Fisher, Ingram, and Ranson (*91*, 1938).

A participation of the posterior lobe of the hypophysis in control of water output was indicated when von der Velden (*382*, 1913) and Farini (*85*, 1913) discovered that its extracts had antidiuretic influence in diabetes insipidus. Pathological evidence also indicated involvement of this structure in the disease. On the other hand, an equal volume of pathological data indicated that structural disturbances in the hypothalamus only were involved, and the effect of posterior lobe extract was considered by many to be a purely pharmacologic one (*cf.* Geiling *107*, 1935). The experimental findings of Camus and Roussy (*42*, *45*, 1913, 1922) of Bailey and Bremer (*8*, 1921) and others also indicated a hypothalamic mechanism. One difficulty in accepting the idea of a hypophyseal function in water metabolism was that totally hypophysectomized animals or patients with complete destruction of the hypophysis usually did not show permanent polyuria. Von Hann (*383*, 1918) suggested that possibly polyuria occurred in the absence of the posterior lobe only provided the anterior lobe remained. Sato (*335*, 1928) and Trendelenburg and Sato (*373*, 1928) advanced evidence to show that the tuber cinereum and hypophyseal remnants (pars tuberalis) took over the function of producing antidiuretic substances in the absence of the hypophysis. An inkling of new light to come appeared in 1924, when Kary (*197*) rediscovered the supraoptico-hypophyseal tract and pointed out that the supraoptic nucleus may be degenerated in diabetes insipidus. This finding was confirmed by Kiyono (*208*, 1925) in a clinical case, and experimentally by Maiman (*251*, 1930). Broers (*30*, 1932) reported the occurrence of diabetes insipidus in dogs after bilateral destruction of the supraoptic nuclei or a lesion of the stalk producing atrophy of the former. Richter (*319*, 1934) found that permanent polyuria followed posterior lobe removal in rats, provided some anterior lobe function was present. This was later confirmed by Pencharz, Hopper and Rynearson (*290*, 1936). Richter (*320*, 1935) also presented convincing evidence that the polyuria, and not the concomitant polydipsia, was primary. Beginning in 1935 Fisher, Ingram and Ranson published a series of papers dealing with experimental polyuria as studied in a very large series of cats and some monkeys. It was found that permanent polyuria follows the production of lesions limited to the hypothalamus provided the lesions interrupted the supraoptico-hypophyseal tract. Histological studies indicated that after such intervention there was atrophy not only of the supraoptic nuclei, but of the pars nervosa of the pituitary, with disappearance of the so-called pituicytes. It was also found that such atrophic glands were lacking in the antidiuretic, pressor and oxytocic principles (Fisher and Ingram *89*, 1936). The melanophore-expanding principle remained present (Fisher *90*, 1937) and was associated with the pars intermedia, which is apparently not under any nervous influence from the hypothalamus. Similar lesions in monkeys also produced diabetes insipidus (Ingram, Fisher and Ranson *169*, 1936). A latent period of some days intervenes between operation and onset of the permanent polyuria, presumably time required for degeneration of secreting elements. Direct removal of the posterior lobe in cats was likewise effective (Ingram and Fisher *167*, 1936), provided not only the infundibu-

lar process but also the stalk and median eminence were removed, since the latter also produce antidiuretic substance. The presence of the anterior lobe appeared to be essential, confirming von Hann and Richter. Further confirmation of the latter point has been offered by Keller, Noble and Hamilton (*206*, 1936) and Dodds, Noble and Williams (*75*, 1937), who found that removal of the anterior lobe from animals with diabetes insipidus abolished the polyuria. White and Heinbecker (*395*, 1937) apparently accepted and confirmed this point of view; more recently, however, White, Heinbecker and Robinson (*396*, 1938) seem to feel that permanent polyuria may occur after total hypophysectomy in dogs. Dodds, Noble and Williams found this also to be true in the rat.

Clinically this conception of the etiology of diabetes insipidus has been confirmed by Biggart (*24*, *25*, 1935, 1936). The conception has not been unopposed, however, since Reichert and Dandy (*318*, 1936) and Mahoney and Sheehan (*250*, 1936) have reported different results. The latter deny that section of the pituitary stalk causes diabetes insipidus in dogs or monkeys, and Keller, Noble and Hamilton have expressed themselves similarily. The latter failed to remove the median eminence, however. Gagel and Mahoney (*105*, 1936) deny that the supraoptic nucleus atrophies following interruption of the stalk fibers. The latter findings are categorically denied by the observations of Hare (*131*, 1937), of Rasmussen (*317*, 1937) and the unpublished results of Magoun (*244*), who found that stalk section in monkeys not only produced polyuria, but also atrophy of the supraoptic nuclei and of the pars nervosa. It is of interest that Morawski (*276*) in 1911 described posterior lobe atrophy after stalk section in monkeys.

Although the above is by no means a complete summary of the various data, the weight of evidence now indicates that the hypothalamus must exert an influence upon the output and thus indirectly upon the intake of water by the body, since in the absence of functional nervous connection between the hypothalamus and the pars nervosa, excretion of water by the kidney becomes relatively unrestrained. The final controlling influence seems to be a hormonal one. The mode of action of the posterior lobe hormone can hardly be discussed here, but it is quite generally accepted as a direct influence upon the kidney (Burgess, Harvey and Marshall *37*, 1933; Klisiecki, Pickford, Rothschild and Verney *210*, *211*, 1932–33; Brull *34*, 1933; Compere *59*, 1933; MacDonald *241*, 1933; Walker, Schmidt, Elsom and Johnston *386*, 1937). It has been clearly shown that the renal nerves are not necessarily involved in either polyuria or antidiuresis. Molitor and Pick (*270–273*, 1924–26) and Mehes and Molitor (*265*, 1927) postulate the existence of a water center in the brain which regulates the water content of the tissues; when uninhibited this center permits passage of water into the blood and thence through the kidneys; upon this water center posterior lobe hormone acts, since injury to the hypothalamus and the use of certain drugs prevents such action of the hormone. This work has been repeated by Theobald (*371*, 1934), who denies the validity of its conclusions. Biggart (*26*, 1937) believes that certain cases of diabetes insipidus fail to respond to pituitrin because of destruction of cell groups in the tuber cinereum upon which the antidiuretic substance may act. In Fisher, Ingram and Ranson's series, however, tuberal damage did not prevent the action of pituitrin.

The question arises: is the innerva-

tion of the posterior lobe through the hypothalamus purely a trophic one or does it offer opportunity for regulating the activity of the former so as to meet the needs of the body. In other words, is there a reflex-hormonal or humoral-reflex-hormonal mechanism for regulating water excretion by the kidney? Several attempts have been made to answer this question. Marx (*260*, 1935) reported that injection of certain substances into the ventricles of dogs with denervated kidneys produced antidiuresis. Theobald and Verney (*372*, 1935), Verney (*380*, 1936) and Rydin and Verney (*330*, 1938) found that water diuresis may be inhibited by pain and fear. Since such results were obtained in animals with denervated kidneys they postulate a neural influence causing the hypophysis to produce antidiuretic substance. Hoff and Wermer (*155*, *156*, 1928) reported that psychic influences as well as administration of diuretic substances caused the appearance of antidiuretic substance in the cerebrospinal fluid; the validity of the analytical determination of such material in body fluids, however, has been questioned (Van Dyke, Bailey and Bucy *378*, 1929; Simon *348*, 1933, *et al.*). Pickford (*297*, 1936), on the basis of indirect evidence derived from water load experiments, suggested that at high water loads the secretion of antidiuretic substance is reduced. Chang, Chia, Hsu and Lim *50*, 1937) reported experiments in which the central end of the cut vagus was stimulated in dogs in which the only connection between head and body was vascular. Such stimulation was found to produce a liberation of acetylcholine and a reflex secretion of pituitrin as shown by a pressor effect which was abolished by removal of the hypophysis or section of its stalk. Pickford (*298*, 1938) observed inhibition of water diuresis in dogs after intravenous injection of small quantities of acetylcholine. On the basis of the work of Chang et al. this antidiuretic effect was ascribed to a release of posterior lobe hormone. Gilman and Goodman (*111*, 1937), following the findings of Heller and Urban (*142*, 1935) and Heller (*143*, 1937) that injected antidiuretic hormone is excreted in the urine, the hormone content of which may be assayed, reported that while normal rats do not excrete any antidiuretic substance, dehydrated rats may do so. On the other hand, hypophysectomized rats when dehydrated fail to excrete any such material. Similar findings have been reported by Boylston and Ivy (*29*, 1938) for rats, and Ingram, Ladd and Benbow (*170*, 1938) for cats. The latter found that cats with diabetes insipidus do not excrete antidiuretic substance even when severely dehydrated. Walker (*385*, 1938), however, did not confirm Gilman and Goodman's findings. Gilman and Goodman interpret their results as showing that the antidiuretic substance is secreted in amounts varying with the need for water conservation. These results are important if they actually demonstrate a neuro-humoral reflex mechanism acting through the hypothalamus. Boylston and Ivy and Ingram, Ladd and Benbow are as yet unwilling, however, to identify positively the antidiuretic substance observed in the urine with pitressin. Unknown toxic substances may appear in urine and may have similar effects.

It is of interest and importance in this connection to note that Gersh (*109*, 1937) has reported the existence of granule-containing "glandular" cells in the posterior lobe, and has observed nerve endings in relation to these cells. The size and number of such cells in rats varies with water intake, increasing in dehydration; they degenerate when the nerve fibers of the stalk are

cut. This histological evidence would seem to support the work of Gilman and Goodman. Further work may elucidate this mechanism further.

The consideration of water exchange brings that of mineral substances into question. So far as the relation of salt excretion to diabetes insipidus and the neural regulation of the former are concerned the experimental and clinical data vary. Leschke (*221*, 1919) found that in diabetes insipidus ingested NaCl was quantitatively excreted in the same time as in normal individuals, but only by an increased urine flow, not by concentration of the urine. Later (*223*, 1933) on the basis of experimental punctures of the hypothalamus he reported variable results, but considered water and salt metabolism to be independent of one another. Bailey and Bremer (*8*, 1921), found that ingestion of excess salt by dogs increased the urine volume and that the salt was excreted more rapidly than normal. Veil (*379*, 1923) and Meyer (*266*, 1926) postulate two types of diabetes insipidus: hyperchloremic and hypochloremic (or normochloremic) types, the first of which alone responds to pituitrin. In the first type, Meyer found that deprivation of fluid resulted in very little elevation of the serum NaCl in spite of concentration of the blood; the same is true after bloodletting and it was suggested that the fluid flowing from the tissues into the blood under such circumstances was hypotonic. The relatively rare hypochloremic types were unable to concentrate the urine when added salt was ingested. In the latter cases there seems to be purely renal disturbance; differences in pathology have not been clearly stated. Weir, Larson and Rowntree (*393*, 1922) observed that treatment of diabetes insipidus with pituitrin causes lowering of the chloride content of the blood and a diminished output of chloride in the urine. Hachen (*126*, 1923) found a very marked fall in blood chloride upon pituitrin administration in his case. In normal animals and patients without diabetes insipidus, the administration of pituitrin has been found to increase the excretion of Na and Cl (Fromherz *98*, 1923, Stehle and Bourne *361*, 1925). The potassium output is also said to be accelerated—to a degree even greater than that of sodium (Stehle *360*, 1927, Engel, McQuarrie and Ziegler *83*, 1933). In Peters' opinion (*295*, 1935) there is a constant washing out of small quantities of NaCl from the blood in diabetes insipidus—this is so slight as to be detectable only upon treatment. Karlson and Norberg (*186*, 1936) expressed dissatisfaction with the classification of diabetes insipidus cases and with previous blood salt studies upon such patients. In their case they noted lack of normal ability to concentrate the urine when excess salt was fed, but noted no change in the blood chloride when fluid was withheld and little elevation of it after salt feeding. Debré, Marie, Nachmansohn and Bernard (*69*, 1936) also found a deficiency in concentrating ability which was restored to normal with pituitrin therapy. Smith and MacKay (*349*, 1936) found no increase in NaCl excretion after pituitrin administration in diabetes insipidus, nor did the sodium balance become negative, as has been reported for normal individuals (Engel, MacQuarrie and Ziegler). The potassium balance also remained positive. Molner and Gruber (*274*, 1934) observed various disturbances in salt exchange in cases with differing types of brain lesions; their results are difficult to evaluate.

From experimental work, Fujimoto (*99*, 1932) reported diminished urine chloride after posterior lobe injury. Tsukuda (*374*, 1933) found that inhibi-

tion of transient polyuria in rabbits by pituitrin injection caused a fall in NaCl output. Broers (*30*, 1932) believed experimental diabetes insipidus to be primarily due to disturbance in salt metabolism, especially of the K and Cl content of the tissues. Sumwalt, Erb and Bazett (*365*, 1935) found reduced chloride excretion after decerebration. Evidence that the posterior lobe and hence presumably the hypothalamus are concerned in salt metabolism has also been offered by Winter, Gross and Ingram (*397*, 1938), who found that while cats with diabetes insipidus had a relatively very short survival time after double adrenalectomy, the serum sodium and chloride remained approximately normal. The blood potassium rose markedly, however. It is well known that serum Na and Cl fall in adrenal insufficiency in normal animals. The same workers have found (unpublished results) that after adrenalectomy in animals in which diabetes insipidus is under control with pitressin the normal blood changes are present and the survival time is prolonged to meet the normal average.

The evidence certainly implies a participation by the hypothalamico-hypophyseal system in salt metabolism. This is presumably a neuro-hormonal influence. Whether or not there is any direct nervous influence upon the tissues in this respect is not clear. Exact elucidation of the finer mechanisms involved is a matter of hope for the future.

The hypothalamus and carbohydrate metabolism: Endocrine factors in carbohydrate metabolism of course deserve, and have received the most attention from investigators of this fascinating subject, especially since the work of Houssay on the hypophysis and Long and Lukens on the adrenal. The rôle of the nervous system should not be overlooked, however, as there is some possibility that certain of the glands of internal secretion concerned in these processes, not to exclude the liver, may be under a certain degree of nervous control. It is not necessary here to discuss the hyperglycemic effects of piqure of the brain stem or of decerebration. We will confine our attention to the hypothalamus. Aschner (*6*) in 1912 reported that injury to the tuber cinereum could produce glycosuria. Weed, Cushing and Jacobson (*392*, 1913) observed glycosuria after puncture of the hypothalamus, and observed that stimulation of the superior cervical ganglion was followed by glycosuria. The latter result has recently been confirmed by Davis, Cleveland and Ingram (*67*, 1935) who, surprisingly enough, noted that this response was abolished by certain lesions of the hypothalamus. Sachs and MacDonald (*332*, 1925) noted transient glycosuria to follow hypothalamic puncture in some cases. Camus, Gournay and LeGrand (*46*, 1925), Beattie, Brow and Long (*18*, 1930), Lewy and Gassmann (*229*, 1935) and others report similar results. Dewulf (*72*, 1931) was unable to confirm the work of Camus and his associates, however. Barris and Ingram (*14*, 1936) observed transient hyperglycemia after production of lesions almost anywhere in the hypothalamus. Such effects are presumably due to irritation and are possibly effected by a hypothalamico-adrenal mechanism (Houssay and Molinelli *160*, 1925).

Elevation of the blood sugar as a result of direct hypothalamic stimulation has been reported by Himwich and Keller (*150*, 1930), Magoun, Barris and Ranson (*246*, 1932) and Miki (*267*, 1932). The latter obtained his results from stimulation in the region of the paraventricular nucleus; subsequent destruction of this region caused hypoglycemia. Högler (*158*, 1932) claims that antipyretic substances cause hy-

perglycemia. Bodo and Benaglia (*27*, 1938) report that sympathin raises blood sugar (*cf.* Magoun, Ranson and Hetherington *248*, 1937).

Tendency to hypoglycemia following production of bilateral lesions in the chiasmal region was reported by D'Amour and Keller (*66*, 1933). Similar tendencies were noted in 10 out of 55 cats with hypothalamic lesions by Barris and Ingram; in nearly all the lesions were suprachiasmal and tuberal. The writer has since seen several cats with such lesions which showed spontaneous hypoglycemic convulsive crises which were relieved by administration of glucose or anterior lobe extract. Houssay (*161*, 1931), however, is emphatic in his statement that hypothalamic lesions are not accompanied by hypoglycemia.

The famous Houssay experiment needs no mention except to state that while hypophysectomy in dogs was found to ameliorate pancreatic diabetes, lesions of the tuber did not. In frogs, however, such lesions did ameliorate diabetes. This was explained as due to an inhibitory action on the pituitary, presumably via the hypothalamico-hypophyseal tract, and presumably due to irritation. Houssay further reported that tuber lesions did not interfere with the blood sugar-raising effect of extracts of the anterior lobe. It is of interest, on the other hand, that Cleveland and Davis (*54*, 1936) report that certain hypothalamic lesions in cats do ameliorate the diabetes which ordinarily follows pancreatectomy, and that Ingram and Barris (*165*, 1936) found evidence that some such lesions may interfere with the action of hypophyseal extracts. Lucke and his coworkers (*239*, 1934) have, of course, held firmly to the suggestion that these substances act through the central nervous system, but Houssay has controverted nearly all of their findings. The question of the suitability or of differences in location of hypothalamic lesions reported by different workers makes a verdict difficult. Other controversial matters enter, also. That some, at least, of the hypophyseal hormones find their way to a site of action in the hypothalamus has been held by a number of workers since the time of Herring (*145*, 1908) (*cf.* Cushing *63*, *64*, 1932). The possible routes are numerous—via tissue spaces, vessels about the stalk, general circulation, cerebrospinal fluid, etc. A hypophyseal portal system as described by Popa and Fielding (*305*, 1930) was an interesting possibility, but Wislocki (*398*, 1937) has not been entirely able to confirm the existence of such a system and argues convincingly that flow of blood in such a portal connection takes place from stalk to hypophysis rather than the reverse. Kylin (*215*, 1935), however, reports finding hyperglycemia-producing substances in the cerebrospinal fluid of hypertensive patients. Pighini (*299*, 1935) has found gonadotropic substances in the hypothalamus, presumably deposited there by the pituitary. Collin, Drouet, Watrin and Florentin (*57*, 1931) claimed that hypoglycemia causes hypersecretion of colloid by the glandular hypophysis and that such colloid is transported to the hypothalamus. Supposed colloid and hyaline bodies in the hypophysis have been said by Gersh and Tarr (*110*, 1935) to be artefacts, although there is no doubt that masses of colloidal material can accumulate in meningeal spaces after injury to the hypophysis. As a sidelight, Scharrer (*337*, 1933), Scharrer and Gaupp (*338*, 1933), Gaupp (*106*, 1935), Peters (*294*, 1935), Roussy and Mosinger (*328*, 1934) believe that the hypothalamus contains neurons capable of producing their own hormones; the evidence is largely cytological and no significance has yet been attached to such secretory capacity.

Some recent work indicates that certain lesions in the hypothalamus may produce a condition resembling somewhat that found in hypophysectomized animals. This includes hypersensitivity to insulin and decreased sensitivity to the hyperglycemic effect of adrenin (Ingram and Barris *165*, 1936). It seems that such lesions, if fairly small and restricted must lie in the anterior hypothalamic region. In many cases they destroy or produce atrophy of the paraventricular nuclei, but the evidence implicating this structure is as yet equivocal. Determination of the exact location and mode of action of such lesions has not yet been accomplished. Do they produce partial suppression of the pituitary by interfering with a nervous pathway to the latter? Do they influence a site of action of the hormones of the hypophysis? Or do they have a direct nervous effect on the viscera and body in general? Insulin hypersensitivity has been undeniably produced by hypophysectomy, by adrenalectomy, by sympathectomy, by spinal cord lesions, and by hypothalamic lesions. We must investigate this matter further.

Clinical evidences of disturbance of carbohydrate metabolism in intra-cranial disease are numerous and need not be mentioned here. Several workers have reported pathological changes in neurons of the hypothalamus and other brain areas in diabetes mellitus (Nicolesco and Raileanu *282*, 1927; Dresel and Lewy *76*, 1921; Marinesco and Nicolesco *256*, 1934; Vonderahe *381*, 1937, et al.). Stief and Tokay (*363*, 1932) found severe changes in the hypothalamus and elsewhere in the brain in insulin intoxication—these resembled pathological alterations found in other types of intoxication and were not specific for insulin.

The hypothalamus and reproduction: Neural factors involved in ovulation and other reproductive functions have recently been discussed by Hinsey (*151*, 1937) and Haterius (*140*, 1937). These factors are closely linked with the anterior lobe of the hypophysis. It should be recalled that at one time it was undecided as to whether hypophysis or hypothalamus was most concerned with such matters as water exchange, gonadotropic activity, etc. That hypothalamic lesions may produce genital atrophy has often been suggested on the basis of experimental and clinical evidence. We need mention here only such older work as that of Aschner (*6*, 1912), Camus and Roussy (*43*, 1920) and Bailey and Bremer (*8*, 1921). The clinico-pathological evidence, while extensive, is often unsatisfactory, for some involvement of the pituitary has usually been indicated or implied. Recently, Cahane and Cahane (*38*, 1936) have reported that genital atrophy occurs in cats after lesions in the diencephalon. Since they found degenerative changes in the anterior lobe in such animals they suggested that the retrogression of the gonads was due to interruption of a nervous influence exerted upon the former by the hypothalamus. The present author (*164*, 1937) has studied the gonads and adrenals from a large number of cats with hypothalamic lesions which have in no way directly affected the hypophysis. The percentage of retrogressive changes in the gonads was small, in the adrenal still smaller. Cats with lesions in the anterior hypothalamus, frequently associated with diabetes insipidus, showed the highest percentage of atrophies. Those in the posterior portion, presumably interrupting a large part of the descending pathways from the hypothalamus were not associated with gonadal or adrenal atrophy. It is the author's opinion that although the anterior lobes in such cases appeared to be normal histologically, the glandular

changes which appeared were probably due to anterior lobe suppression in spite of the fact that cats which were hypersensitive to insulin did not always have gonadal atrophy. How such suppression is brought about, unless by interference with the innervation of the gland, and why it does not occur more uniformly cannot be said at present. There is a possibility of some remote relationship between the lesions producing diabetes insipidus and the gonadotropic activity of the anterior lobe, because no estrus-type ovaries were found among those from animals of this type, even though many of the cats were killed during the breeding season. Such a relationship probably rarely exists in the idiopathic form of the disease in man. On the other hand, cats with other types of hypothalamic lesions have been observed to breed and bear young which were nursed and cared for adequately. Harris (*132*, 1937) observed genital atrophy after sectioning the pituitary stalk in rabbits. Hinsey (*151*, 1937) reported similar results, but Brooks (*32*, 1938) found no significant change in the gonads after stalk section in his experiments. Section of the stalk must interfere to some extent, and for a time at least, with the blood supply of the gland.

Innervation of the anterior lobe, however, is not essential to the production of gonadotropic hormones, especially of the follicle-stimulating principle, since Schweitzer, Charipper and Haterius (*344*, 1937) noted continuous estrus in guinea pigs from which the hypophysis had been removed and hypophyseal transplants placed in the anterior eye chamber. The ovaries showed no mature follicles and the absence of cyclic activity in these animals was ascribed to failure of periodic release of luteinizing hormone (Haterius *140*, 1937).

The mechanisms involved in ovulation in animals which ovulate only after coitus has made an interesting problem which involves the hypothalamus and associated structures. Such animals include the ferret, the rabbit and the cat. Marshall and Verney (*258*, 1935) carried out stimulation of the brain through the skull in rabbits, with electrodes in the mouth and under the skin of the nape, using 30 volt, 50 cycle alternating current; this caused convulsions, but was followed by ovulation after 17–24 hours, and pseudopregnancy was a sequel. No localization was possible, and the possibility of direct stimulation of the hypophysis cannot be excluded. Presumably such stimulation led to the release of luteinizing hormone necessary for ovulation. Harris (*132*, 1937) applied electrical stimuli directly to the hypothalamus—in the tuber cinereum and the posterior region not far from the red nucleus. The current used was a direct, pulsating type (vide Hess *147*, 1932), with a unipolar electrode in the brain. Ovulation followed such treatment if the doe were in heat, even, as in one case, if the superior cervical sympathetic ganglia were removed. Although it is difficult to exclude spread of current to the hypophysis, Harris believed the latter to be activated by way of a nervous pathway. Haterius and Derbyshire (*139*, 1937), Haterius (*140*, 1937), also used intracephalic stimulation, with bipolar needles and faradic current, and were able to limit the amount of spread definitely. Ovulation was induced by stimulation of a seemingly definite area in the preoptic and septal region, although precise data as to localizaton are not yet available. It is hard to account for the differences in localization found by Harris and by Haterius, except on the basis of spread of current in one or the other instance. Motor responses accompanying stimulation were flexor rigidity of the hind limbs and pelvis, shortening of the trunk and

elevation of the tail,—this was uniform, but was said to have no probable functional relationship to ovulation. Action potentials led off from the area in question showed definitely increased activity when olfactory stimuli were applied. In this connection, Rosen and Shelesnyak (*324*, 1937) induced pseudopregnancy, with ovarian luteinization, by irritation of the nasal mucosa with silver nitrate in rats. In neither Harris' nor Haterius' experiments were the effects of stimulation studied after section of the pituitary stalk. The work of Brooks (*32*, 1938) is of importance in this connection. This worker found that while cervical sympathectomy did not prevent normal ovulation in response to coitus, section of the pituitary stalk did, in spite of the fact that the rabbits mated frequently. Incomplete section of the stalk failed to prevent ovulation. It was said that disturbance of the blood supply to the hypophysis was not of a nature to prevent reproductive function, and the rabbits remained in normal condition without changes, such as hypoglycemia or increased sensitivity to insulin, which would indicate anterior lobe deficiency. Injection of pituitrin, adrenalin and mecholin failed to produce ovulation, indicating that a direct nervous influence and not a humoral mechanism is involved. Brooks also was able to identify nerve fibers in the anterior lobe of normal rabbits; such fibers could not be found in glands the stalks of which had been cut. According to Brooks some doubt still exists, however, as to whether cutting the infundibulum might prevent the passage of some chemical excitant from the hypothalamus to the anterior lobe. This question may be answered by the production of intrahypothalamic lesions interrupting hypothalamico-hypophyseal nerve connections without disturbing the circulation of the gland. Possibly in the rabbit such lesions would not prevent the onset of estrus which must be present in order for ovulation to occur. In the writer's experience, cats with lesions interrupting the hypothalamico-hypophyseal connections have not been observed to enter estrus. Perhaps an artificial estrus could be induced, making such preparations suitable for experimentation. It is of interest that Foster, Haney and Hisaw (*94*, 1934) prevented ovulation in the rabbit with atropin.

We thus have strong evidence that certain elements of reproductive activity are associated with nervous mechanisms related to the hypothalamus, preoptic area and hypophysis. There is also some evidence that such mechanisms are concerned with parturition in some animal forms at least. Ingram and Fisher (*168*, 1937) and Fisher, Magoun and Ranson (*92*, 1938) have observed that pregnant cats with diabetes insipidus have difficulty delivering their young and frequently succumb during parturition. Other cats with hypothalamic lesions but without diabetes insipidus have been observed to breed and to deliver their kittens normally. On the other hand, Smith (*351*, 1931) and Pencharz and Long (*291*, 1933) failed to find that removal of the posterior lobe interfered with parturition; anatomical evidence of complete removal was, however, inadequate. Keller and Hamilton (*204*, 1937) found that dogs bred and whelped normally after stalk section—only one of these animals had a moderate diabetes insipidus. Women with diabetes insipidus are said to have no unusual difficulty in parturition. However, two recent cases (Soule *353*, 1937; Greene and Gibson *115*, 1938) were under effective treatment with posterior lobe powder, which may have replaced any posterior lobe deficiency. While there has hitherto been no real evidence to show that the oxytocic factor of the posterior lobe secretions plays an essential part in normal parturition, the difficulty ex-

perienced by cats wtih atrophic posterior lobes, associated with the fact that such glands are deficient in oxytocic principle (Fisher and Ingram *89*, 1936) has led Fisher, Magoun and Ranson to suggest that this hormone is necessary in some animals at least. The present writer has been able to induce parturition and carry it through with nearly normal celerity in one cat with marked diabetes insipidus by the use of obstetrical pituitrin, but many more such experiments are needed, with the establishment of adequate controls, to make the finding significant. One must accept these observations on polyuric cats with some reservation pending further studies to establish the normalcy of ovarian function in such animals.

The hypothalamus, behavior and sleep: It has been pointed out by Ranson (*312* 1936) and others that the responses to direct stimulation of the hypothalamus are of a nature which if observed in normal waking cats would be associated with anger, fear or some such emotion. These responses, including pupillary dilatation, erection of hair, sweating, elevation of blood pressure, cessation of intestinal movements, elevation of blood sugar are all of a so-called "affective nature" which in the normal animal would occur along with motor activity of a definite type—struggling, clawing, biting, etc. The hypothalamus may be concerned with integration of the sympathetic phases of response to stimuli tending to produce behavior of an emotional type. While emotional behavior may be considered in higher animal types to be the result of definite psychic reactions and interpretations of sensations, it should not be forgotten that emotional types of behavior appear in animals of very primitive cortical development. Rage and fear reactions are themselves primitive, are associated with mechanisms of self-defense and self-maintenance (capture of food), and may be well integrated despite the absence of a well developed neopallium. Behavior characteristic of rage has been observed to be particularly unrestrained in decorticate animals such as those of Goltz (*113*, 1892) Rothman (*325*, 1923) and Dusser de Barenne (*78*, 1919) and has been recently discussed in detail by Bard and Rioch (*13*, 1937). Head and Holmes (*141*, 1911) found that in patients with interruption of cortico-thalamic connections ordinary sensations are overlaid with a sort of "feeling tone" associated with emotional reactions judged to be due to lack of cortical restraint. Cannon and Britton (*49*, 1925) were responsible for utilizing cat preparations in which the brain stem was transected in the upper part of the diencephalon for the study of the visceral aspects of so-called pseudoaffective behavior. When subjected to physical restraint these animals displayed all the signs of blind rage. Because of the absence of cortical and presumably psychic elements this behavior was called "sham" rage. Bard (*10*, *11*, 1928, 1930) made a detailed study of such preparations in the acute state and found that this condition occurred only when removal of the upper parts of the brain left the posterior portion of the hypothalamus intact. The intensity of the rage reaction was presumed to be due to loss of inhibitory activity ordinarily exerted by the cortex. Later study (Bard and Rioch *13*, 1937) showed similar behavior in chronically decorticate cats, in which it could be elicited by relatively insignificant stimuli. This pseudoaffective behavior was not observed after transection caudal to the hypothalamus. Bard (*11*, 1930) points out differences between certain pseudoaffective elements in the reactions of decerebrate cats (Bazett and Penfield *15*, 1922), which are "isolated items of behavior", and sham rage of decorticate animals which "is astonishingly intense and possesses a

width and energy of expression that makes it unmistakably the counterpart of intense fury in the normal animal". Fulton and Ingraham (*101*, 1929) observed chronic rage in cats with bilateral prechiasmal lesions. Keller (*199*, 1932) on the other hand reported that rage could readily be induced in cats after transection well down in the midbrain. On the basis of experiments such as have been described and of stimulation experiments, Ranson (*312*, 1936) concluded that the hypothalamus is the center for the integration of the visceral and somatic components of emotional expression. He was careful to point out that "this does not mean that rage and fear as conscious emotions are associated with the activity of the hypothalamus alone", and that it is "necessary to emphasize . . . the fundamental distinction between emotional expression as a type of reaction and emotional experience as a phase of consciousness". Further discussion of these matters has been given by Cannon (*47*, 1927) and Bard (*12*, 1934).

Since such forms of behavior may be produced by release from cortical control or by direct stimulation of the hypothalamus the effects of lesions so placed as to interfere with the descending connections of the hypothalamus become of interest. Ingram, Barris and Ranson (*166*, 1936) found that bilateral lesions in the caudal part of the hypothalamus produce a sort of catalepsy in cats. These animals are free of emotional reactivity and display a peculiar plastic type of muscle tonus so that they maintain for long periods bizarre induced postures, similar to those maintained by catatonic patients. As will be mentioned later, the early phases of this syndrome are associated with somnolence. The tonus changes are not improbably related to damage of the upper part of the midbrain, for while monkeys with similar hypothalamic lesions but less significant injury to the mesencephalic tegmentum show somnolence and loss of emotional reactivity they do not develop catalepsy. The emotional changes in hitherto wild monkeys (Ranson *312*, 1936) were striking—they became tame, their faces were blank and expressionless and showed no fear or anger. A catalepsy somewhat similar to that described above has been observed to result from administration of bulbocapnine to animals such as the cat (*see* Ingram and Ranson *172*, 1934, for references), and it is interesting that cats which have shown cataleptic behavior because of hypothalamic lesions are much more susceptible than normals to the "catatonizing" effects of this drug.

It is perhaps not without interest that the present writer has frequently seen marked changes in personality, if the term may be applied to animals, which give a picture the reverse of the cataleptic type already mentioned, in cats with hypothalamic lesions. Such animals, formerly tame and friendly, become savage beasts which may or may not show fear. Some will attack a man with little hesitation. They snarl and crouch and resemble small tigers rather than the proverbially friendly tabby, and may lose the daintiness of habit characteristic of domestic cats. In these animals there is no injury to the cortex. Whether corticohypothalamic connections are disturbed has not been determined. The lesions are usually toward the rostral and medial portions of the hypothalamus, sparing the lateral portions. It may be recalled that it is the latter from which stimulation may elicit signs of emotional excitement. Cats with perfectly normal behavior may have strikingly similar lesions, however, which renders the localization problem difficult.

Further evidence of almost exclusively hypothalamic participation in these matters so far as the diencephalon is concerned, is shown by the effects of

thalamic lesions in monkeys (Ranson *312*, 1936). These animals show little change in behavior and retain their capacity for emotional expression. Apparently extensive destruction in the dorsal thalamus need not produce symptoms of the sort associated with disturbances in the hypothalamus. Stimulation of the hypothalamus in unanesthetized cats has been carried out, as previously mentioned, by Kabat, Anson, Magoun and Ranson (*182*, 1935), and more recently by Massermann (*261*, 1938). The responses were typical of wild rage and fear. Massermann also observed sham rage in response to restraint in some cats with extensive hypothalamic destruction. Others showed apathy and lack of emotional response. Spontaneous emotional manifestations were observed only in cats with unilateral destruction.

It has been suggested that the hypothalamus may be related to epilepsy (Morgan and Johnson *279*, 1930), and Kabat, Anson, Magoun and Ranson observed convulsive seizures in unanesthetized cats receiving strong electrical stimuli in the hypothalamus. Other instances of convulsions upon stimulation or irritation of the hypothalamus have been previously mentioned. It is a question whether these effects are localizable in the hypothalamus or are attributable to impingement upon more remote structures. Such experiments have been discussed by Wortis and Klenke (*399*, 1933), who doubt the existence of a convulsion center. The present writer has never observed spontaneous fits in cats with a variety of hypothalamic lesions, aside from those connected with hypoglycemia. That vegetative disturbances of the sort associated with hypothalamic activity occur in epileptic seizures, however, is beyond question.

It has been stated that somnolence occurs in cats and monkeys with bilateral lesions in the caudal portions of the lateral hypothalamic areas. It is difficult to study somnolence in cats, but there was no doubt about the condition in monkeys (Ranson *312*, 1936, and observations in press). This sleep was reversible, since the animals could be awakened easily, but the period of wakefulness was short. The somnolent condition sometimes lasted for weeks. The lesions were of a sort calculated to sever the descending connections of the hypothalamus, but in no way did they interfere with the major sensory pathways to or within the thalamus, nor did purely thalamic lesions of wide extent cause somnolence, contrary to the findings of Spiegel and Inaba (*356*, 1927). Furthermore, thalamic nuclei were not disturbed. As a result of these experiments Ranson suggests that the emotional drive furnished by the hypothalamus is an important factor in maintaining the waking state.

The clinical literature contains numerous references to somnolence associated with lesions of the diencephalon. Adler (*1*, 1924), Economo (*81*, 1930), Fulton and Bailey (*100*, 1929), Guillain, Bertrand and Périsson (*124*, 1925), Haenel (*127*, 1925), Hirsch (*152*, 1924), Levin (*225*, 1929), Lhermitte and Tourney (*230*, 1927), Lucksch (*240*, 1924), Marinesco (*255*, 1921), Parker (*287*, 1923), Pette (*296*, 1923), Rowe (*329*, 1935), Davison and Selby (*68*, 1935), Souques, Baruk and Bertrand (*354*, 1926) Weisz (*394*, 1933) and others have made contributions to this subject. Attention was drawn to sleep as a symptom by Economo following the great epidemic of encephalitis lethargica. In studying the pathology of this disease Economo found lesions in the transition region between diencephalon and midbrain and postulated the existence there of a sleep center. The general literature on the cause and regulation of sleep is fairly voluminous. Besides a fair amount of clinico-pathological work and some experimental

work, there has been a vast amount of armchair philosophy devoted to the matter. The oldest authorities such as Purkinje, considered sleep as due to a physiological interruption of afferent pathways at a central point, and Mauthner (*263*, 1890) located this point in the central gray of the caudal part of the third ventricle and upper part of the aqueduct on the basis of pathological observations. Economo, however, has pointed out that while this area may be crucial, it has no connection with higher sensory areas. Also, sleep considered as merely due to shutting off extraneous stimuli brings out the inference that the normal state of the brain is sleeping—that waking is only brought about by exogenous or endogenous stimuli. The sleep of sucklings is an example. Kreidl and Herz (*213*, 1924), found no difference in the sleep curves of normal and deaf and blind people. A wide variety of sleep theories exist. The idea of hypnotoxins in a pure sense is no longer widely held. That sleep is a matter primarily involving the cortex was proposed by Marburg (*254*, 1926), Pavlov (*289*, 1927), Lucksch (*240*, 1924), Nachmansohn (*280*, 1927) and others, although it is well known that decorticate animals sleep (Kleitman and Camille *209*, 1932). Others, led by Economo, support the idea of a central sleep center which may or may not be directly related to the cortex. Such a center would possibly take the form of an active, primary regulatory mechanism, probably vegetative, or it may merely be a station for a sort of transformation or rearrangement of incoming impulses, according to some interpretations. The concept of a center regulating sleep is hard to controvert because of the frequency of diencephalic lesions associated with disturbances of sleep. Kleitman, however, does not think such a concept is essential. All the contributions about theories of sleep will not be discussed in this communication. The evidence from experimental as well as from pathological studies points to the existence of some mechanism associated with the vegetative areas of the diencephalon having to do with sleep.

It is necessary to mention the work of Hess (*146*, 1931), who was able to induce apparently normal, reversible sleep in unanesthetized cats by applying damped, pulsating direct current through electrodes fixed in the ventral part of the diencephalon and preoptic area. No definite localization of structures involved has been forthcoming. Hess attempted to relate the sleep producing mechanism to the parasympathetic portion of the vegetative system, since suppression of the sympathetic with ergotamine was said to lead to sleep. The involvement of cholinergic mechanisms is also indicated by the intraventricular injection of acetylcholine (Dikshit *73*, 1934). Demole (*70*, *71*, 1927), Lafora (*217*, 1931), Marinesco, Sager and Kreindler (*257*, 1929) and Brunelli (*35*, 1932) produced sleep by injection of small amounts of calcium salts into the hypothalamus or the third ventricle. A relation between a sleep promoting mechanism and that for heat regulation was noted in hibernating animals by Uiberall (*375*, 1934). These examples together with those already mentioned will serve to justify the theoretical consideration of a functional relationship between the hypothalamus and the control of sleep. It has been indicated that Ranson postulates the hypothalamus as the source of an emotional drive necessary for maintaining the waking state. The terms are perhaps unfortunate, as it is difficult for one to associate a calm, serene wakefulness with emotion. What is undoubtedly meant, however, is a toning effect on the activity of the higher brain structures—an effect which, if excessively active due to release from or activation by the cortex, may lead to the

outward and inward expressions of emotion, but which is ordinarily exerted at a level below that producing marked somatic and vegetative changes. No doubt other structures are concerned, the cortex beyond all, and the means by which they act and interact will remain obscure until more information is obtained. In the meantime, the mere fact of locating in a vague way a part of the whole apparatus among the vegetative areas of the hypothalamus is an essential step in our progress.

Conclusion

The variety of functions attributable to such a small structure as the hypothalamus seems almost incredible. The evidence for many of them, however, is convincing and who knows what new viewpoints will yet be added by future research. The contributions made clearly indicate that this portion of the brain contains important integrating mechanisms for the so-called vegetative functions. Many of these mechanisms produce their effects by influencing lower, subordinate complexes. In turn, the hypothalamus is undoubtedly under a certain measure of control by higher regions, including the cerebral cortex. It has been pointed out, also, that the hypothalamus may itself play a part in regulating the activities of the cortex, and students of psychic activity would do well not to ignore this possibility. The author is aware of the pitfalls lurking in this line of endeavor, but hardly needs to stress the importance of a conservative viewpoint, with due emphasis on facts rather than speculation. Not alone in this field, but along other lines is there need for more investigation. The hypothalamic mechanisms concerned with sleep and with emotional expression, with the control of body temperature in warm-blooded animals, with the activities of the viscera, etc., are by no means entirely clear. A great deal of work remains to be done upon the possible rôles of the hypothalamus in the metabolism of mineral substances, carbohydrates, fats and proteins. In the latter case a practically virgin field is open. Much has been done in relation to water metabolism but as yet not all of the features of this problem are clear. The relation of the hypothalamus to reproduction is another fascinating field. The reader will have noted that attempts at localization of functions in the hypothalamus have met with little success except as to a few general areas. So far as specific cell groups are concerned, the nucleus supraopticus is the only one definitely linked with a certain activity. Perhaps no precise localization will be possible in many instances—the group or mass pattern reactions suggested by Beattie may be the answer. At any rate, so much has thus far been accomplished that one can only feel that as the loose threads are caught up, new ideas and viewpoints developed, and new tools for working devised, a concise, comprehensive statement as to the real functions of this region will one day be possible.

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NOTE WITH REGARD TO TEMPERATURE REGULATION

STEPHEN WALTER RANSON

IN AN ARTICLE on "The Hypothalamus" published in the Ergebrisse der Physiologie (*41:* 56–142, 1939) Drs. S. W. Ranson and H. W. Magoun summarize their observations on the regulation of body temperature as follows: The hypothalamus and the preoptic region play leading rôles in the regulation of body temperature. A receptive mechanism specifically sensitive to heat lies in the preoptic and supraoptic regions. When the temperature of this part of the brain becomes too high the cat pants, and sweat appears on the foot pads. Probably vasodilatation also occurs but no tests were made to show this. The location of the efferent center or centers for the heat loss mechanism is not known except that the motor correlation center for polypneic panting lies behind the hypothalamus probably in the mesencephalon. From the preoptic and supraoptic region a pathway leads backward through the lateral part of the hypothalamus. Bilateral destruction of the region sensitive to heat or of the path leading backward from it through the lateral hypothalamus causes a loss of ability to keep the body from overheating. In cats with such lesions panting does not occur when the rectal temperature is raised to 41°C.

Body temperature is prevented from falling too low by heat formation and conservation. Vasoconstriction and fluffing of the hair conserve heat. These are sympathetic reactions and are under the control of the sympathetic centers in the hypothalamus. Shivering and increased tension of the muscles are chiefly and perhaps wholly responsible for the increased heat production resulting from exposure to cold (DuBois, 1936). Shivering, although it involves somatic musculature, appears to be controlled by the hypothalamus and to be abolished at least temporarily by properly placed hypothalamic lesions.

Large lesions in the hypothalamus cause a pronounced loss in the ability to keep the body temperature up to normal and the farther back in the hypothalamus they are placed the more pronounced is the loss. Moderate sized lesions in the hypothalamus cause such a loss only if they are placed in the caudal part of the lateral hypothalamus. The effectiveness of lesions in this location is due to the interruption of the chief descending pathway from the hypothalamus which enters the mesencephalon after passing through the region lateral and dorsolateral to the mammillary bodies.

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SYMPOSIUM ON HYPERTENSION

SOME CARDIOVASCULAR MANIFESTATIONS OF THE EXPERIMENTAL NEUROSIS IN SHEEP

O. D. ANDERSON, RICHARD PARMENTER and HOWARD S. LIDDELL*

DURING THE INVESTIGATION of conditioned motor reflexes we found it possible to produce in sheep an enduring behavioral disorder which we have identified with the experimental neurosis in dogs described by Pavlov. A sheep trained to stand quietly in a loose harness learns to discriminate accurately between signals indicating a forthcoming mild electric shock to the foreleg and other signals indicating the withholding of the usual shock. It executes precise rhythmical flexion movements of the foreleg in anticipation of the shock at the positive signal and remains quiet at the negative signal.

Certain relations between signals for shock and for no shock we have found to precipitate the experimental neurosis. In general, when positive and negative signals are closely similar, when long delayed reactions are attempted, and when regular alternations of signals for shock and no shock are separated by equal rest periods the "neurotic" behavioral state may develop.

Among the several manifestations of the experimental neurosis in the sheep (over-reaction to stimulation, extreme restlessness, irregular and rapid respiration[1]) we have observed and studied during the last two years a marked and apparently permanent disorder of the heart's action. In the present report it is our intention to describe this disorder in some detail.

The observations were made not only in the conditioned reflex laboratory under carefully controlled conditions of stimulation, but also in the animal quarters under conditions wherein the animals were comparatively free to move about among their fellows and were apparently unaware that they were being observed.

During the first part of the work the heart was examined by means of the stethoscope; later we have used successfully a cardiotachometer devised and constructed by one of us (R.P.). Electrocardiograms have been taken in both normal and neurotic animals and work is in progress on the study of the blood pressure in sheep with the Van Leersum carotid loop.

In order to observe the heart sounds and to determine the character and rate of the heart beat without disturbing the animals by our presence we employed a long distance stethoscope. The chest piece, held in place over the area of the apex beat by a web strap, is connected with the ear piece in the observation room by a long rubber tube running through the wall of the quiet animal room. When the heart was ex-

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[1] Anderson, O. D. and Liddell, H. S. Observations on experimental neurosis in sheep, Arch. Neurol. & Psychiat., *34:* 330–354, Aug. 1935.

amined in the barn where the animals were quartered a similarly extended stethoscope was used, the observer being concealed in a small room inside the barn. Under both circumstances the animals could be seen by the observer through a small reducing lens in the wall. The heart sounds were almost as clearly audible through the long tube as through the conventional short tube.

The cardiotachometer[2] has proved useful throughout the experiments in providing objective records of the pulse rate. It was designed especially to rule out the action potentials from skeletal muscle so that, under proper conditions, a clear-cut "picket fence" type of pulse record can usually be obtained even during the vigorous movements of the conditioned motor reflex.

The Rapidity, Irregularity and Sensitivity of the Heart's Action in the Experimental Neurosis in Sheep: One of the most striking and obvious signs of the disorder is the great *rapidity* of the pulse in the neurotic animals as compared with the normal.

In addition to repeated observations of this fact in our flock of 26 sheep, the pulse was studied systematically in two normal and three neurotic sheep under natural and under laboratory conditions. The normal and experimentally neurotic animals had received approximately the same training in the conditioned reflex laboratory. In the examinations carried out in the animal quarters the pulse rate was determined hourly throughout the day and night for three days, and on each day at noon and at midnight counts were made every minute for 30 minutes to determine the pulse range. During the periods of observation the animals were noted at times to be walking slowly about, at other times to be eating or to be lying down and ruminating. They seemed to pay little attention to outside noises yet acceleration of the pulse in the neurotic sheep often followed noises in the night such as the creaking of a windmill.

In the laboratory, the observations were made only during the day. The procedure in handling the animal to be tested was the same as that employed in preparation for the usual conditioned reflex tests and all of the sheep were thoroughly accustomed to the routine. The sheep was led onto a low platform in the sound-deadened animal chamber and straps, suspended from a beam above, were adjusted loosely under each limb. It was allowed to eat from a bucket of oats on the platform. No conditioned stimuli were applied. As soon as the preparations were completed the pulse was counted every minute for a period of 15 minutes. The sheep was then released.

The results of the tests made under the two conditions, barn and laboratory, are summarized in Table I. In the animal quarters the average pulse rate of the three experimentally neurotic animals, during the daylight hours, was 12 beats per minute faster than that of the normal ones, while during the night hours it was 9 beats per minute faster. In general, the average rate for both groups was somewhat lower during the night than during the day. It can be seen at once (column 1) that the pulse range of the neurotic group definitely exceeded that of the normal. The greatest range in the normals was 24 beats (56–80) in sheep #11, trained for 7 years; the greatest range among the neurotics was 48 beats (72–120) in sheep #8, also trained for 7 years.

At noon and at midnight, when the pulse count was made every minute for 30 minutes, the rate was found to vary enormously in the neurotics. The

[2] The instrument and its use under these and smiliar conditions will be described by R. Parmenter in a later paper.

TABLE I

THE PULSE RATE OF NORMAL AND NEUROTIC SHEEP UNDER NATURAL AND LABORATORY CONDITIONS

	In Animal Quarters						In Laboratory	
	Hourly Diurnal Observations						Observations Every Minute for 15 Minutes	
	Range of Pulse		Average Pulse Rate		Observations Every Minute for 30 Minutes. Range of Pulse		Range of Pulse	Average Pulse Rate in 15 Min. Period
	Day	Night	Day	Night	Noon	Midnight		
Normal Sheep								
Sheep #1	68– 84	64– 84	72	72	68–76	68– 76	80– 88	85
Sheep #11	56– 80	56– 72	70	65	60–72		74– 88	80
			Average 71		compare with		Average	82
Neurotic Sheep								
Sheep #7	68– 96	60– 88	84	72	76–96	60– 80	107–152	129
Sheep #8	80–104	72–120	87	89	76–88	80–112	88–136	111
Sheep "D"	60–100	60– 88	78	71	60–80	60– 80	76– 92	83
			Average 83		compare with		Average	107

greatest variation, 42 beats per minute, was observed at midnight in the markedly disturbed sheep #8 and occurred within three minutes. The variation in rate among the normal animals was moderate, being at the highest 12 beats in sheep #11. The range during the night was about the same as during the day for all animals except neurotic sheep #8, the latter showing the highest range at midnight.

When the results obtained in the barn are compared with those obtained in the laboratory, the influence of the preparatory manipulation and of the laboratory room itself upon the sheep can easily be seen. The average pulse rates of each group (underscored for comparison in columns 3 and 8) show that when an average normal sheep is taken from the barn to the laboratory and allowed to stand quietly in the harness the pulse is increased by 11 beats per minute (from 71 to 82); but when the sheep with experimental neurosis is subjected to the same laboratory environment the pulse is increased 24 beats per minute (from 83 to 107), twice the increase observed in the normal. In one sheep (see Table II) pulse rates were determined over a period of six months. During this time experimental neurosis developed and a concomitant development of tachycardia was observed.

The pulse of the neurotic sheep is not only rapid, it is also *irregular*, and in some cases premature beats are definitely observed. The type of irregularity most frequently encountered may be described as an alternation between a very slow and a very rapid pulse, a change which may take place within 2 to 5 seconds. Thus the pulse may be 70 and within a few seconds it may accelerate, for no apparent reason, to a level of 100 and then drop back to 60. See Figs. 1 and 4. Such fluctuations may occur once or even twice in a minute. We have observed this irregularity in the animal quarters as well as in the laboratory under condi-

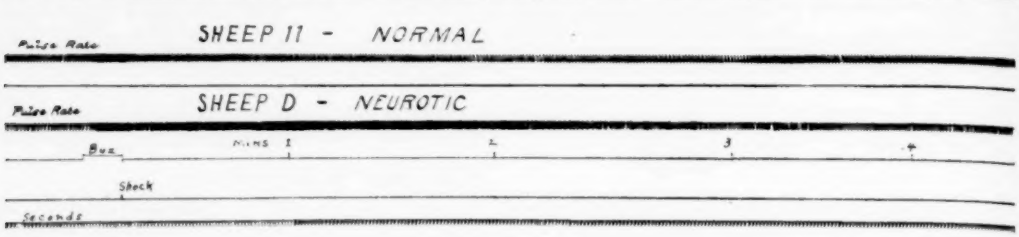

FIG. 1. The effect of a conditioned stimulus followed by a brief electric shock to the foreleg (unconditioned stimulus) on the pulse rate in a sheep with experimental neurosis. The bottom line records time in seconds. The upstroke on the line above signals the application of the shock. The upstroke and downstroke on the next line above show the beginning and end of the conditioned signal (the sound of a door buzzer). The two upper lines record the pulse by means of a signal magnet in circuit with a telegraph key which the observer taps as he hears the heart beats through the stethoscope. Long practice has minimized the unavoidable errors inherent in this crude method of recording the heart beat. The top line shows the inconsiderable change in pulse rate in the normal sheep as compared with the considerable and lasting effect of conditioned and unconditioned stimulation on the frequency and regularity of the pulse in the neurotic sheep.

tions of quiet. At times the period of spontaneous tachycardia has lasted as long as a minute. Sometimes the brief periods of acceleration when observed in the laboratory are noted either to precede or to occur coincidently with spontaneous flexion movements of the reaction limb, characteristically exhibited by the neurotic sheep in the constant 5 minute rest periods between conditioned stimuli (see Fig. 4). At other times they are not correlated with any observable movement or stimulation.

In one animal, sheep "D", in which the experimental neurosis first appeared in 1930 and has been studied continuously to the present writing, October 13, 1938, the most marked irregularities are observed. At times, with the stethoscope or with the cardiotachometer, a disturbance of the rhythm can be detected which is suggestive of a gallop, *i.e.*, beat . beat . . beat . . . beat . beat . . beat. This disturbance was observed during the experiment shown in Fig. 1 and accounts in part for the irregularity of the pulse in sheep "D" between the second and third minutes of the test. Comparing the pulse of the neurotic with the normal sheep frequent irregularities appear during and following conditioned stimulation when the heart rate is rapid. The stethoscope reveals premature beats. They are also detected, although relatively infrequently, when the neurotic animal is standing quietly in the barn among the other sheep.

The tachometer record of the beats sometimes shows a coupled rhythm as seen in Fig. 2. This often lasts throughout the period of stimulation and for

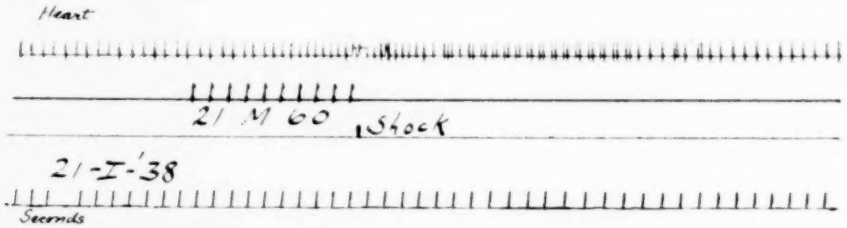

FIG. 2. A cardiotachometer record of coupled rhythm in the sheep induced by a conditioned stimulus (metronome at 60 beats per minute) followed by a brief shock to the left foreleg. The top line records the pulse. On the line below is indicated the duration of the conditioned stimulus. The upstroke on the next line below signals the shock and the bottom line records time in seconds. The presence of the coupled rhythm is confirmed by the stethoscope during registration with the cardiotachometer. The first beat of each pair is clearly accented.

as long as one minute afterward, gradually being superseded by the normal rhythm. Even after the single beats reappear an occasional double beat occurs.

In the electrocardiographic records the T wave becomes inverted during and following the conditioned stimulation (sounding of buzzer or metronome). When the electroencephalograph is used the record also shows a definite inversion of the T wave initiated by the stimulus. The inversion is very pronounced during the first minute after the stimulus has been withdrawn but the wave, at the end of 3 or 4 minutes, assumes its upright position again.

In the experimentally neurotic sheep the heart is extremely *sensitive* to conditioned and other stimulation. The pulse rate may be accelerated by 10 to 40 beats per minute during the presentation of the conditioned stimulus followed by the mild shock applied to the reaction leg. The acceleration usually follows almost immediately upon the beginning of stimulation, *i.e.*, from 1 to 3 seconds after the buzzer or metronome has been sounded,[3] and the rapid pulse may persist for as long as 3 minutes after the stimulus has ceased. In the normal animal, on the other hand, the rate may increase only moderately, *i.e.*, by 5 to 6 beats per minute during the same stimulation. The acceleration is gradual and reaches its height after about 5 seconds of the 10 second stimulus; the pulse actually becomes somewhat slower in some cases just before the end of the stimulus period. When stimulation is stopped the slightly increased pulse usually persists for no longer than 3 to 5 seconds and then slows to normal. These facts are graphically shown in Fig. 1.

[3] The conditioned stimulus is usually continued for 10 seconds.

The neurotic sheep's heart is so sensitive that even a slight tap upon the wall of the experimenter's room during the conditioning tests will often cause marked acceleration. The same effect is produced by a great diversity of causes, such as opening the door of the animal's room, approaching or touching the animal, taking away the pan of oats, the bleating of sheep in the adjoining pasture, the barking of a dog nearby, and so on. The heart action in the normal sheep remains relatively unaffected by such moderate stimulation.

When a negative conditioned stimulus is applied (one never reinforced by shock) there generally occurs in the neurotic sheep a quick initial acceleration of the heart rate whether conditioned leg movement occurs or not. This increase is, however, usually followed by a decrease of rate to the prestimulus level, as soon as the animal "recognizes" the negative nature of the signal.

From our experience in listening to the heart sounds of a large number of our sheep there seems to be nothing in the sounds themselves to distinguish the neurotic sheep from the normal animals and in neither group have heart murmurs been heard.

A study of the electrocardiograms from the sheep at rest (not being experimentally stimulated) shows no essential difference in the heart complex between the neurotics and normals.

A Case History Illustrating the Origin and Development of Cardiac Disorder in the Experimental Neurosis in Sheep: Sheep #52, a female, born March 1, 1935, was reared at the Cornell Physiological Field Station. Conditioned reflex experiments were not begun until November 1935 when the animal was 8 months old. It is a hybrid animal, being a cross between the Shropshire and the Cheviot breeds. In its physical

characteristics the Cheviot strain is predominant. Its behavioral characteristics observed from the first, long before training began, were also strikingly like those of the Cheviot. The animal, in common with this breed, showed a type of behavior in the pasture and in the barn which sheep farmers themselves have perhaps described best by the phrase "just naturally wild and crazy". In our experience the farmers' observations have been accurate. As a well-grown lamb this animal was constantly bleating. It seemed excessively shy of the people about the Field Station and resisted in the most vigorous fashion any attempts to catch it. Of course normal sheep, before they have been handled, also resist such attempts, but not as vigorously and as persistently as this animal. Its shyness as a lamb is well illustrated by the following behavior consistently observed. If, for some reason, we wished to herd the flock into the barn, every sheep would docilely follow the leader through the door except this animal. It frequently came last and stood outside the door looking watchfully through it. On seeing the attendant in the barn it would turn about and run back to the pasture at once. It had then to be rounded up individually and driven into the building.

The first experiments in which the animal was employed were not designed primarily to study the manifestations of the experimental neurosis. A conditioned motor reflex was formed to the sound of a buzzer which was reinforced by a shock to the left foreleg (the reaction leg). A negative conditioned reflex was next formed to a doorbell sound. A differentiation was quickly established. Tests of the conditioned reflexes were made intermittently from November 1935 to November 1937 with long periods of time in which the animal was not tested. During this two year period the behavior in the laboratory including the conditioning tests was identical with that of any normal sheep.

In view of its atypical reactions outside the laboratory, the possibility of producing an experimental neurosis in this animal was investigated. A procedure was adopted which had served to bring about the condition in previous animals; namely, the alternation between positive and negative conditioned stimuli separated by rest periods of exactly *equal* duration, in this case 5 minute periods. The conditioned stimuli heretofore used with this animal had been separated by rest intervals of variable duration (1 to 5 minutes).

The experiments now to be reported were carried out in an experimental room unfamiliar to the animal. The standard procedure of stimulation adopted was as follows: buzzer 10 secs. (shock)—5 min. pause—bell 10 secs. (no shock)—5 min. pause—buzzer 10 secs. (shock)—5 min. pause—bell 10 secs. (no shock)—animal released. This unvaried routine was repeated three or four times a week from November 19, 1937 to April 27, 1938.[4] A differentiation between metronome rates, 120 beats per minute (positive) and 50 beats (negative), was then attempted. The routine of presentation was the same as in the case of the buzzer and bell. The metronome tests extended from April 27, 1938 to June 16, 1938.

The behavior was quite normal during the first few weeks of testing with the new buzzer and bell routine. This fact is shown graphically in Fig. 3. About two months after the tests were started the sheep began to exhibit the typical premonitory signs of the experimental neurosis. Three months

[4] The authors wish here to express their thanks to Mr. A. Tainton-Pottberg for technical assistance rendered during this time.

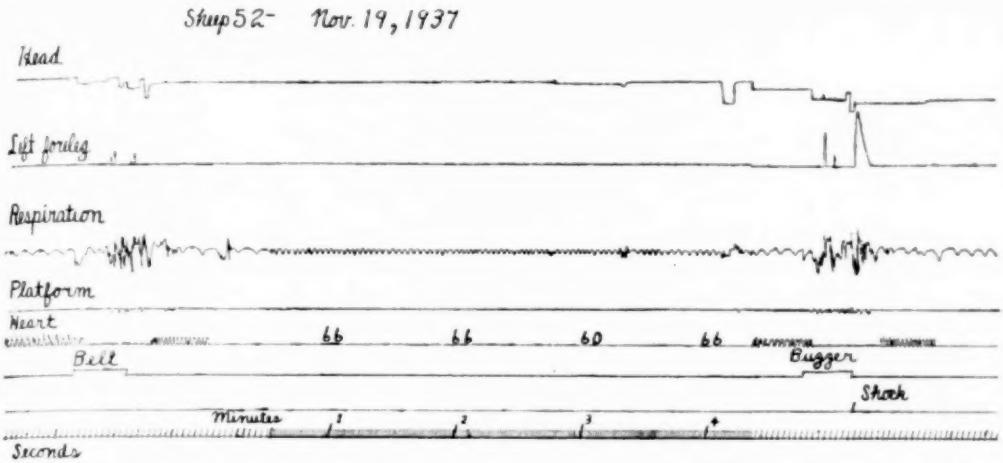

FIG. 3. A sample of the behavior of a normal sheep in the Pavlov frame during a typical test of its conditioned reflexes. The lines from top to bottom record head movement, movement of the left foreleg (to which the brief shock is applied), respiration, movement of the sheep on its platform, heart beat (numbers indicate rates determined each minute), conditioned stimulus, shock and time in seconds.

later the neurosis was completely developed. See Fig. 4.

No evidence of clear differentiation either between buzzer and bell or between metronome 120 and 50 beats per minute was observed.

Table II shows the result of the experimental routine upon the heart's action. The effect upon the sensitivity of the heart and upon the pulse range was gradual, developing over a period of 5 to 6 months. Since this is the case, the general trend is best seen by means of sample protocols taken at different stages in the development of this disorder.

The motor reactions of the animal during stimulation finally became so violent, when the neurosis had reached its height, that the pulse record of the cardiotachometer was occasionally disrupted. Accordingly we have taken pulse counts before the onset of the signal and after its cessation, at which time the motor reaction had also ceased. However, as we have pointed out, the accelerating effect of the stimulus persists in the neurotic animal for some time after the stimulus has been withdrawn.

Inspection of Table II reveals that, at the beginning of the experiment, the increase in pulse rate following stimulation and the range of the pulse are well within the limits shown by the normal sheep; namely, an augmentation of 9 beats per minute and a range

TABLE II

SHEEP #52—CASE HISTORY

Date	Conditioned Differentiation	Increase in Pulse Rate following Stimulation (Beats per min.)*	Pulse Range in Rest Intervals between Stimuli (5 minutes)
Nov. 19, 1937	Buzzer & Bell No differentiation	9	60– 72
Feb. 17, 1938	Buzzer & Bell No clear differentiation	15	78– 90
Apr. 27, 1938	Buzzer & Bell No clear differentiation	31	88–114
May 31, 1938	Met. 120 & Met. 50 No differentiation	25	78–100

* The increase in the pulse rate is determined by a count of the pulse during the 10 second periods immediately preceding and immediately following the conditioned stimulation. The figures given represent the average of the day's four stimuli.

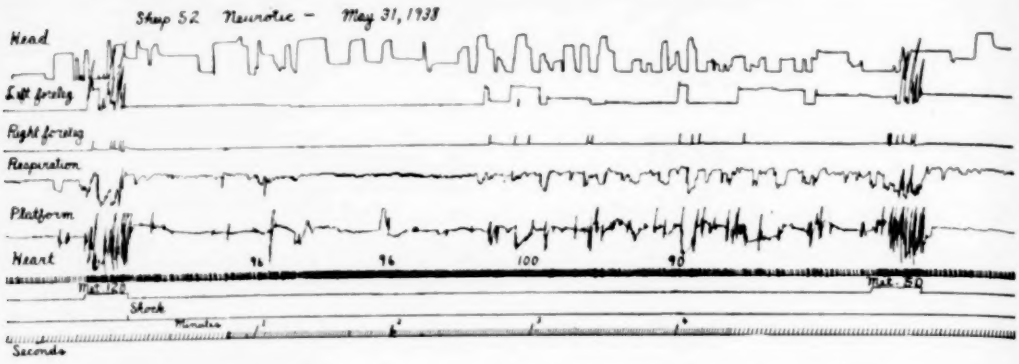

FIG. 4. A sample of the behavior of the same sheep following the onset of the experimental neurosis. The record is to be interpreted as indicated in Fig. 3. The heart is here recorded by means of the cardiotachometer.

of 60–72. Three months later, on February 17, 1938, when all signs indicated that a definite experimental neurosis had developed, the increase in the pulse rate due to stimulation was now 15 beats per minute and the pulse range had increased to 78–90. At this stage the animal could not withhold the leg reaction when the negative stimulus was presented, although the reaction was generally less than that elicited by the positive stimulus. Two months later, on April 27, 1938, the increase in rate had advanced to 31 and the range to 88–114. Still no clear evidence of differentiation was observed. The neurosis was at its height.

We now began the metronome experiment to see whether or not changing the nature of the stimuli to be differentiated would have any effect upon the neurotic manifestations. After one month of testing, on May 31, 1938, the increase in the stimulated pulse rate was 25 beats and the range was 78–100. This slight diminution in the values does not seem significant in view of the fact that all the other neurotic manifestations remained unchanged.

SUMMARY

Sheep in which an experimental neurosis has been developed reveal, upon examination, a cardiac disorder which is characterized by a rapid and irregular pulse and by extreme sensitivity of the heart's action to conditioned and other stimulation. Rapid increases of rate occur in response to mildly startling stimuli which have no effect upon the pulse of normal sheep. Spontaneous variations of rate are observed both in the barn and in the laboratory. Conditioned stimulation produces a considerable and long continued increase in pulse rate associated with premature beats and sometimes with coupled rhythm. A case history depicts the gradual onset of these cardiac manifestations in a sheep during the development of experimental neurosis.

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SYMPOSIUM ON HYPERTENSION

THE PRESENT CONCEPTION OF "ESSENTIAL" HYPERTENSION

A PHYSIOLOGICAL AND CLINICAL CORRELATION

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INTRODUCTION

THE SUBJECT of hypertension has many aspects involving different lines of study which must be correlated into a coherent whole. To ignore the fundamental laws governing the physiological control of blood pressure is as serious an error as to neglect the fact that patients with high blood pressure have mental conflicts and emotions. Therefore, the following discussion will begin with the clinical physiology of blood pressure regulation, proceed to the clinical picture of hypertension, and terminate with comment on the possible mechanisms involved in this important disorder.[1]

I. CLINICAL PHYSIOLOGY OF BLOOD PRESSURE CONTROL

The functions of the circulation in the higher animals, including man, require no detailed elaboration. Suffice it to say that a finely balanced interplay of nervous and hormonal messages achieves the necessary coordination between the demand and the supply of blood in the community of specialized organs and tissues. In the adjustment of the blood flow to meet the needs of the moment, peripheral regulation by the terminal blood vessels is the predominant factor. This peripheral resistance, in relation to cardiac output, determines the level of arterial blood pressure. The etiology of high blood pressure must, in the last analysis, be found in the factors which initiate and maintain an abnormally high peripheral resistance.

Adequate blood flow in the capillaries requires the pumping action of the heart, the elastic reservoir effect of the aorta and the large arteries to help convert the intermittent flow from the heart into the more physiological continuous flow in the capillaries, and the possibility of pressure changes by alterations 1) in the minute output of the heart (change in heart rate or stroke volume) or 2) in the calibre of the terminal vessels—the arterioles, capillaries and venules. Changes in the viscosity of the blood or in the elasticity of the arteries affect average blood pressure very little.

Normally, the resistance of the terminal vessels or flood gates varies not only with the needs for blood of the organ containing them, but with the demands of other organs in the body. In the splanchnic area the range of adjustment is large; in the heart, the brain and the lungs, the blood supply is less independent of the general level

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[1] Bibliographical references are not given since the literature is reviewed in this issue.

of blood pressure. The arterioles in the muscles, skin, kidneys and some of the ductless glands, are intermediate in their responsiveness. Arteriovenous anastomoses, vascular reservoirs such as the liver, spleen, subcutaneous tissues and lungs, and other devices add to the preciseness and complexity of blood pressure regulation by peripheral mechanisms.

Physical and Chemical Influences Controlling the Peripheral Blood Vessels: Increase in peripheral resistance may be brought about by such physical factors as increase in tension of a muscular organ (heart or viscus) or of a secretory gland; by pathological reduction of the lumina, of the terminal vessels, if enough units are involved; or by the effects of cold. Chemical influences include vasoconstrictor hormones (pituitary and adrenal) and the host of vasodilators of local tissue origin, as histamine and choline derivatives, adenylic acid compounds, lactic, phosphoric and carbonic acids, and unidentified tissue extracts. Renin, obtained from the kidneys, is a pressor substance widely studied at present.

Nervous Influences Controlling the Peripheral Blood Vessels: The nervous control of the peripheral blood vessels is perhaps more important. This may function locally by way of the axone reflex, as in the response to temperature and certain chemical substances. Somewhat wider control of the local blood supply is mediated through the peripheral autonomic ganglia or the dorsal root ganglia. For general changes in blood flow or pressure, the entire sympathetic and parasympathetic system must come into action, as well as parts of the cerebrospinal nerves. Correlating all these effector pathways are the so-called vasomotor nerve centers which, in man and other primates, are to be found at several levels—in the spinal cord, the medulla, the hypothalamus, thalamus, the subcortical and even the higher cortical layers of the brain. Each of these centers is responsive to all the humoral and nervous messages available, including the blood supply and metabolism of the center itself. Each higher center integrates activities of a more complex nature than the lower centers and can bring about not only a nervous but also a hormonal discharge for peripheral action. To these centers come impulses along afferent nerves from the special sense organs during conscious activity, from end organs in the skin and organs of locomotion, from all the viscera, and, most important, from the cardiovascular tree itself. The vascular end organs are not limited to the carotid artery and the aorta, but are distributed in the coronary vessels, the pulmonary vessels, the great veins near the heart, in the auricles and in the abdominal vessels.

The Integration of the Influences Controlling Blood Pressure: Physical, chemical and nervous influences collaborate in the control of the peripheral terminal vessels, the arterioles, venules and capillaries. Perhaps the most important is the nervous regulation, which functions by means of local axone reflexes, of longer pathways in the autonomic nervous system, and of so-called nerve centers situated in practically all levels of the spinal cord and brain. It is significant that the highest centers for vasomotor control are closely linked with those nerve cell groups which determine voluntary and emotional bodily responses.

The relative constancy or homeostasis of blood pressure implies the activity of some integrating mechanisms to correlate the multiple influences at play upon the vascular system.

Recent experience has shown that this homeostatic property resides primarily in the end organs located in the

blood vessels themselves. The most important end organs are those located in the carotid sinus and the root of the aorta. They have been called the buffer or moderator mechanisms. It has been shown that when the afferent nerves from these end organs are severed, the fluctuations in blood pressure are excessive, the reflex moderating influence which these nerves normally exert being lost. From this point of view, it follows that high blood pressure can result from one or two types of causes: 1) Loss of ability of the moderator mechanism to temper the ordinary strains of physical, mental and emotional activity of everyday life which are attended by elevation of blood pressure; or (2) excessive stresses exceeding the ability of the moderator mechanism to cope with them. Such stresses may be normal or abnormal in character.

An understanding of the principles controlling the relation of the responses of the sense organs of the moderator mechanism to the qualities of the stimuli acting upon them, will make the subject clearer. These end organs obey the same laws that govern other sense organs in the body. Thus, the responses of the moderator end organs are increased a) as the magnitude of the rise in pressure in the vessels in whose walls they are located is increased, and b) as the rate of this pressure rise is augmented. If the elevation of pressure persists, it is associated with a progressively diminishing response, since these end organs, like all end organs, show fatigue. Thus a persistent or chronic elevation of pressure is much less effective than an abrupt transitory one in stimulating the moderator end organs. This is the inherent weakness of the moderator mechanism. It is not as well attuned to chronic as it is to acute stimulation. Another fact of importance is that stimulation of the moderator end organs is not directly by the pressure elevation within the vessel lumen but rather by the stretching of the vessel wall which accompanies the pressure rise. Hence, when arteriosclerosis involves the vessel wall and diminishes its distensibility, the effect of a given pressure rise will be less than normal. It may be that arteriosclerosis of the vessel wall is one example of the diminution in the efficiency of the moderator mechanism during the aging process. Other examples of such loss may be associated with diseases involving this apparatus, leading to a destruction of some of the moderator end organs or their afferent nerves, or to a decreased sensitivity of the entire moderator mechanism. Inherited weakness of the moderator mechanism may also exist in certain family strains. The weakness of the moderator mechanism in the above condition may remain occult as long as only light strains are exerted upon it, and no blood pressure elevation may appear. High blood pressure may develop, however, when such an inherited weak moderator mechanism is put to undue strain or when it is further weakened by superimposed aging or disease processes.

The stresses to which the moderator mechanism is exposed vary considerably among different individuals, groups, and races. For example, the amount of physical exertion may vary markedly. Thus, if a man were exerting himself as in a marathon run, the stress upon the mechanism would be beyond its ability to handle and the blood pressure would stay up. In a similar fashion, it is possible that the moderator mechanism would be unable to cope with continuous marked emotional tension or frequent repetition of periods of emotional tension. Again, if because of disease one of the nerve centers regulating blood pressure were constantly hyperactive in elevating the blood

pressure, the moderator mechanism might not be able to neutralize its effects. Or, if some humoral secretion of a pressor character, such as seems to be produced in certain diseases of the adrenals and in renal hypertension, were constantly being liberated sufficiently in excess of its rate of destruction, the moderator mechanism might not be able to counteract the effect. A similar over-strain would result if there were a lack of production or an excessive destruction of depressor substances.

An assay of the recent literature seems to indicate that the moderator mechanism is not defective in hypertension but that it is exposed to excessive strain with which it cannot cope. However, it may turn out that some forms of high blood pressure are produced by an inherent, perhaps hereditary, weakness of the moderator mechanism. Surely, we will not be far afield if we view all types of hypertension as the result of a disturbance in the ratio between the strain upon the moderator mechanism and its ability to cope with such strain. Both an increase in the strain and a decrease in the ability of the moderator mechanism to cope with it would lead to the same net result—maintenance of the blood pressure at a higher level.

The Hemodynamics of Hypertension: The hemodynamics which occur in an acute elevation of blood pressure are not equivalent to those in long established hypertension. The hemodynamics must be studied, therefore, in essential hypertension in man or in its equivalent, the chronic hypertension produced in the dog by renal ischemia. Recent work has shown that in chronic hypertension, the circulating blood volume is unchanged and the venous pressure is normal, except when heart failure complicates the picture. The capillary pressure in the majority of instances is normal, although occasionally reports of elevated capillary pressure in hypertension have appeared. The blood viscosity is normal except when the hypertension is complicated by a polycythemia. The heart rate, systolic output, minute volume output of the heart, and the circulation time are normal unless heart failure is present. The blood flow through the extremities is also within the normal range, which suggests that the peripheral resistance in the extremities increases step by step with the rise in blood pressure.

No direct evidence is available on the blood flow in other parts of the body, although some recent work has tended to show that in established experimental renal hypertension the venous outflow of the kidney on direct measurement is within the normal range. Calculations based on the creatinine clearance in essential hypertension in man also show that the renal blood flow is normal. In the kidney the changes in vascular resistance apparently parallel the changes in the blood pressure. Inferentially, it would seem that the blood flow in the lungs would also be normal, because the blood flow in the lungs in a stabilized condition is equal to that in the systemic circuit, and in hypertension the latter is normal. In the blood vessels of the brain and heart, unless we assume some direct constriction as a result of the pressure elevation, it might at first glance be argued that the blood flow increases in these organs since their vessels are poorly supplied with vasomotor nerves and are not as reactive as the other peripheral vessels. However, the development of arteriosclerosis in these vessels would tend to cut down this excessive blood flow. In the case of the heart, the hypertrophy which develops as the hypertension persists would also tend to reduce the blood

flow per gram of muscle. How these various factors balance out is not known, although the presence of cerebral vascular insufficiency and coronary insufficiency shows that late in the hypertensive state the flow may become inadequate. If the blood flow in the coronary circuit and in the brain circuit is increased early in hypertension, and evidence on this point is sadly lacking, this must be at the expense of the blood flow in the splanchnic area. However, the final answer to these speculations on blood flow distribution must await further investigation.

From the available knowledge, it would appear that in established chronic hypertension the fundamental hemodynamics are unchanged. Changes ensue either because of the complicating arteriosclerosis, the development of heart failure, or the superimposition of renal insufficiency. While the hemodynamics do not deviate from normal, this is brought about by an increased work on the part of the left ventricle, because the pressure against which the left ventricle must pump is augmented. This will lead to an increased energy cost for the cardiac activity but presumably without changing its mechanical efficiency. The long persistence of hypertension brings about an increase in the muscle mass of this chamber to enable a greater energy liberation. Often, this is not accompanied by an appreciable clinical or fluoroscopic evidence of cardiac enlargement because it is unassociated with dilatation. The condition of hypertrophy sometimes can be first recognized in the characteristic changes in the electrocardiogram which indicate left ventricular preponderance.

II. Clinical Aspects of "Essential" Hypertension

From the clinical viewpoint, "essential" hypertension presents many problems, some obvious and others not superficially apparent. Briefly, one must consider 1) the criteria for an elevated blood pressure; 2) the delimitation of the disease, "essential" hypertension, from other hypertensive states; 3) the clinical course of the disease, including the "malignant" phase; 4) the clinical etiology of hypertension, with special reference to associated diseases; 5) the "hypertensive personality"; and 6) the problems of treatment.

The Normal Blood Pressure and Hypertension: Many statistical insurance studies are available concerning the blood pressure of healthy individuals of varying age, sex, height, and weight. Admittedly, both the systolic and diastolic pressures rise gradually with increasing age. However, the mean ultimate levels reached in normal old age do not surpass the upper limit of the normal range for any given healthy adult in the middle third of life. Therefore, most clinicians have accepted a systolic pressure of 140 to 150 mm. and a diastolic pressure of 90 to 95 mm. as indicative of borderline or early hypertension in middle-aged or younger individuals. In the case of older subjects, a systolic pressure of 160 mm. is usually accepted as the minimal hypertensive level in order to allow for the individual fluctuations about the higher mean level. It is apparent at once that the diagnosis of early hypertension is fraught with serious difficulties, especially if the individual's previous blood pressure level is unknown. Not only must age and, probably, weight, be taken into account, but all the other variables upon which any given blood pressure reading may depend; for example, the position of the patient, the time of day, the effect of food, exercise, or emotion, the temperature of the room, the manner of application, inflation, and deflation of the blood pressure cuff, the

physician's selection of the significant figures. To conclude, then, that a man of 40 with a systolic pressure of 150 and a diastolic of 95, on a few measurements over a brief period, has early hypertension is not justified any more than a diagnosis of hyperthyroidism on the sole basis of several basal metabolic rates of +15 per cent. If it is known that the systolic pressure was never above 110 to 120 mm. in previous examinations under reasonably similar conditions, the higher figures now obtained acquire considerably more significance. Whether the individuals with occasional moderately elevated blood pressure readings, in the absence of obvious emotional disturbance, form a group predisposed to hypertension at some later period, cannot be decided on the available evidence. The possibility of "potential" hypertension must be considered. During puberty or the menopause it is often difficult to make a diagnosis of early hypertension.

In individuals over 55 or 60 two factors operate synergistically to produce an elevated systolic pressure, but counteract one another in their effect on the diastolic pressure. The systolic pressure may be increased by a combination of diminished elasticity of the aorta and whatever other pressor influences operate in normal old age. On the other hand, the normal increase in diastolic pressure, with age, may be neutralized or even inverted by decreased elasticity of the aorta. In the latter case there develops the common "arteriosclerotic" hypertension, with high systolic and pulse pressures, a normal or abnormally low diastolic pressure, and elongated and tortuous peripheral arteries; but with relatively little of the cardiac hypertrophy or enlargement of "essential" hypertension, and with little progression of the disease. Obviously, this clinical picture is entirely different from "essential" hypertension and must be excluded rigidly in clinical or pathological studies of essential hypertension. Failure to observe this precaution has already resulted in much confusion.

Another source of error is hyperthyroidism. In younger individuals the hyperkinetic personality, flushed face, and moderate increase in systolic pressure may lead to a diagnosis of hypertension unless the normal or low diastolic pressure and the other signs and symptoms of hyperthyroidism are given due recognition. The differential diagnosis may be much more difficult in the older age groups because the two conditions may be combined, or the hyperthyroid state may exist in a submerged form. Close attention to the diastolic pressure values should prevent confusion with "essential" hypertension.

The Definition of "Essential" Hypertension: Originally the term "essential" hypertension was synonymous with "non-renal" hypertension and implied the absence of organic kidney disease, at least in the early stages of the hypertensive state. In recent years, the discovery of the association of hypertension with certain suprarenal tumors, pituitary basophilism, congenital coarctation of the aorta, lead encephalopathy, certain "toxemias" of pregnancy and a few other conditions, has led to the removal of these small groups from the category of "essential" hypertension. The exclusion of the larger group of "arteriosclerotic" hypertension has already been discussed. After all this pruning, there still remains an enormous number of middle-aged individuals with unexplained hypertension, constituting a major health problem and one of increasing importance as more and more people escape the mortal dangers of infectious diseases and live on into the fifth, sixth, and seventh decades.

It is obvious that both the systolic and the diastolic pressures must be elevated to justify a diagnosis of "essential" hypertension. Also, a progressive elevation of the blood pressure is implied. The rate of this progression probably varies extremely and is to a large extent still an unknown quantity for lack of adequate clinical observation. The presence or absence of cardiovascular or other symptoms is of little consequence in the diagnosis of "essential" hypertension. Cardiac, retinal, cerebral, or renal findings are, however, of great value in the estimation of the probable duration of hypertension and the ultimate outcome.

The Clinical Course of "Essential" Hypertension, Including the "Malignant" Phase: The end results of hypertensive disease are well known. Approximately two-thirds of the affected individuals develop cardiac insufficiency, including coronary accidents. This may happen at a time when kidney function is still normal, although the urine usually shows changes suggestive of renal arteriolosclerosis. About 15 to 25 per cent of the patients suffer from cerebral accidents, often without obvious cardiac or renal failure. Only 5 to 10 per cent of hypertensive individuals end their course in primary renal failure, or uremia, although renal insufficiency secondary to cardiac failure is not uncommon in advanced hypertension. It should be emphasized that none of these serious sequelae of hypertension ordinarily occur within a brief period from the known onset. In most cases the blood pressure has been elevated for ten or more years before signs of organic disease appear. Cardiac failure, if recognized and treated early (*i.e.*, as left ventricular weakness), will often respond favorably and its victim may carry on for a considerable number of years. Heart disease in individuals past age 50 is predominantly secondary to hypertension.

The pathology of hypertension adequately explains the late clinical syndromes. In the middle stages of hypertension the only abnormalities at autopsy are some degree of left ventricular hypertrophy, medial hypertrophy of small arteries in the splanchnic organs, and, to a lesser extent, in the voluntary muscles, and focal arteriolosclerosis, chiefly in the kidneys. The first two findings are undoubtedly secondary to the increased peripheral resistance and elevated blood pressure; the renal arteriolosclerosis may be a secondary or concomitant process. With progression of the hypertensive state, renal, cerebral and retinal arteriosclerosis increase to varying degrees in different individuals, producing the composite clinical pictures. Cardiac failure may be found with or without coronary disease. Vascular changes associated with age may be difficult to separate from those attributed to the hypertensive state.

There is unfortunately too little autopsy material from the earlier stages of hypertension, but enough to indicate the possibility of the total absence of organic vascular disease. If this holds true for a more complete study, it will have an important bearing on the theory of the etiology of hypertension. Recently there has been an unjustified return to the old hypothesis that organic arteriolar disease in the kidneys is the initiating factor in "essential" hypertension. Factual evidence for this view is at present entirely inadequate.

The more important, because possibly reversible, earlier phases of hypertension are only beginning to attract interest and close study. The relatively asymptomatic course in many patients prevents medical supervision. On the other hand, once hypertension has been

discovered more or less accidentally, the patient's reaction to the knowledge of this dreaded disease may be expressed not only in symptoms strongly suggestive of a neurotic state but in artificially abnormal blood pressure values. The physician measures the blood pressure often in order to evaluate the progress of the underlying disturbance; the patient, anxious about his blood pressure, hyperreacts to the stimulus and produces a higher pressure than he would if he did not know he had hypertension. Often, tachycardia, flushing, and other signs of autonomic nervous stimulation betray the patient's anxiety. These are not necessarily eliminated by a preceding period of rest. It only requires the inflation of the blood pressure cuff to undo the relaxing effect of physical rest. For these and other reasons the fluctuations of blood pressure in hypertensive patients are difficult to interpret in relation to the course of the disease. In many, perhaps most, patients the blood pressure levels found under ordinary conditions may be more nearly maximal than average. Comparison with levels obtained under basal metabolic conditions may prove of value.

During the course of hypertensive disease in individuals under the age of 50, the "malignant" phase is most likely to occur. The term "malignant hypertension" has primarily a prognostic significance. Individuals with "malignant" hypertension should not survive this diagnosis more than a year or two. Great confusion has arisen among clinicians because of the further implication that the entire course of the disease, or the total duration of hypertension, is only a matter of a few years. Actually, in many patients careful inquiry will reveal the presence of hypertension for a number of years preceding the onset of symptoms. The total duration of the disease may run into one or more decades. The age distribution of individuals in the "malignant" phase still supports the view that a special type of hypertensive disease exists, based, perhaps, on the greater opportunity for vascular stimulation and response in younger subjects. However, the process is more than functional. When the "malignant" phase is diagnosed, there is abundant organic vascular disease in the usual sites for hypertensive pathological changes. This finding, too, speaks against a brief total duration of the hypertensive state.

As to the criteria for the diagnosis of the "malignant" phase, it is obvious that an unduly high blood pressure and an age under 50 are insufficient grounds. To these must be added some reasonable duration of the hypertensive level, certain retinal changes of both chronic and acute types, and definite signs of renal arteriolosclerosis and arteriolonecrosis. Cardiac and cerebral manifestations are often added to the picture, to produce in a single individual the entire gamut of findings ordinarily distributed among several cases of "benign" hypertension in the late stages. The transitions between the "benign" and "malignant" stages of hypertension are shrouded in ignorance. Exogenous and endogenous factors are probably involved, but their elucidation awaits further clinical and experimental observation.

The Clinical Etiology of Hypertension: The definition of "essential" hypertension by the process of excluding known organic diseases of the kidneys or other organs furnishes only negative evidence regarding the clinical etiology of this extremely prevalent condition. More positive support for the theory of a general metabolic derangement in hypertensive patients seems to be supplied by the association of hypertension with obesity, diabetes

mellitus, hypertrophic arthritis, gout, the menopause, and certain other diseases or disturbances. In all of these attempted correlations two fallacies are apparently involved: 1) Simple coincidence is mistaken for intimate relationship; thus, in the last third of life it is not remarkable that obesity should coexist with hypertension or other common diseases in those individuals who have been fortunate enough to satisfy their appetites in previous years. 2) It is assumed that more is learned or understood about a disease by attributing it to an associated condition of which equally little or less is known.

It is peculiar, in view of the neurogenic theory of hypertension held by many investigators, that hypertension is rarely observed in patients with Raynaud's disease or with other typical vasoneuroses. It is also noteworthy that, in spite of the common belief in the rôle of infections of one sort or another in the etiology of hypertension, the only infectious diseases definitely known to produce hypertension are acute (hemolytic streptococcus) glomerulonephritis, pyelonephritis, and periarteritis nodosa. In all three diseases, the kidneys are seriously involved, and the hypertension is not "essential". As a rule, many patients with hypertension are in excellent general health, are free from signs of infection, and give no history of an unusual incidence of infections.

The clinical theory that hypertension is a disease of civilization, afflicting individuals of families constitutionally predisposed to excessive vasomotor reactivity, seems to have considerable support in the known clinical data on hypertensive families and in the remarkable infrequency of hypertension among African Negro natives and other uncivilized races. While it may be justifiable to doubt the value of the clinical statistics on the blood pressures of various natives, the incidence of hypertension in the American urban Negro is a remarkable phenomenon and scarcely to be explained by interracial mixture. Obviously, accurate information must be obtained on the question of the geographical distribution of hypertension between rural and urban populations of similar age groups and racial constitution. In the United States, such a comparative study of white and negro races, urban and rural, should prove of immense value in testing the rôle of certain alleged factors in the etiology of hypertension.

The mechanism whereby civilization could produce hypertension in the predisposed individuals will be discussed in the third section of this paper. It is interesting that civilization has also been blamed for the prevalence of psychoneuroses. The possibility of vasomotor disturbances originating as neurotic reactions and eventuating in hypertension as a "habit" must be considered seriously. However, in spite of neurotic symptoms in some hypertensive patients, their general activity, external drive, and often successful adjustment to life's problems are in striking contrast to the psychoneurotic's behavior. The knowledge of hypertension may in itself be productive of neurotic anxiety reactions. To unravel some of these clinical tangles, intensive psychological study of hypertensive individuals, with adequate controls in the same age groups and social levels, is urgently needed.

The "Hypertensive Personality": The characteristic features of this type of personality are indicative of increased psychomotor activity. The afflicted individual is hyperkinetic in all ordinary activities. He often has an hypertrophied conscience and strives for perfection. He displays excessive autonomic responses to minor emotional stimuli and may exhibit a sanguine or

choleric temperament. While it is true that this type of personality is often found in hypertensive individuals and, in many, has definitely preceded the onset of hypertension, there are numerous exceptions—hypertensive patients without this personality, and vice versa. In some instances the personality seems to have developed secondary to the hypertensive state or to the cerebral vascular changes associated with it. Obviously, psychogenic factors active earlier in life must have an important bearing on the evolution of the "hypertensive personality". The possibility that the same processes are also responsible for hypertension later in life cannot be dismissed lightly. However, evidence on which to base any definite conclusions is lacking. Regardless of the origin of the changes in the personality, there is no doubt that the hypertensive patient is often harmed by his excessive psychomotor activity.

The Problems of Treatment: In our ignorance of the etiology of "essential" hypertension, treatment becomes a difficult matter. There is so little known or understood of what is to be treated. Yet, if a safe and effective depressor drug were available, there would be no hesitation in administering it to all patients with "functional" hypertension. However, the use of such a drug after organic changes are well established may be detrimental to the patient if, as a result of lowering the blood pressure, cerebral, cardiac or renal insufficiency should develop. It would be very advantageous to be able to depress the effector mechanism of hypertension, not only to eliminate the symptom, the elevated blood pressure, but to determine what other effects of the underlying disease remained. There is still considerable argument concerning the cause and effect relationship of hypertension and certain organic changes that appear in the course of the disease.

The principles of treatment have varied from time to time, depending on the concepts of etiology. Strenuous dietary treatment was in vogue during the period of belief in the organic renal origin of all hypertension. As the hereditary and constitutional viewpoints became popular, general hygienic measures came to the fore. With the renewed emphasis on renal vascular constriction, functional or organic, as the fundamental basis for human hypertension, in analogy with the Goldblatt experimental hypertension, surgical attempts to denervate the kidneys or to establish collateral circulation have become logical procedures. Perhaps, as has been suggested by Goldblatt, the beneficial results of splanchnicectomy or thoracico-lumbar sympathectomy are secondary largely to renal vasodilatation. Whatever the ultimate value of these surgical procedures may be, it is clear that insufficient experiments have been carried out on young individuals with early hypertension, in whom the best results should be obtained. However, anything short of complete restoration of the blood pressure to a normal or subnormal level, after a surgical denervation of the kidneys in early hypertension, would have to be considered as a therapeutic failure in view of the slow and variable natural progress of the disease at this stage.

If hyptertension is believed to be due to, or closely associated with, unresolved emotional conflicts of one sort or another, thorough analysis and psychotherapy are of prime importance. Progress in this field has been slow because of the time-consuming nature of the treatment and the small number of patients under the care of any one psychiatrist. Furthermore, interpretation of the published results is rendered

difficult by the improper selection of the clinical material in some instances and the inadequacy of control observations in other cases. Close cooperation between the internist and the psychiatrist is essential not only for the psychosomatic approach to the study of hypertension, but for the avoidance of the numerous pitfalls and errors of fact-finding and judgment so likely to occur in any one-sided study of chronic human disease.

III. Description of the Mechanism of "Essential Hypertension"

The Importance of Peripheral Arteriolar Narrowing: As already mentioned, a survey of the literature indicates that essential hypertension is caused by systemic arteriolar narrowing. It is not generally appreciated that a relatively minute change in the circumference of the individual peripheral blood vessels is accompanied by a large increase in peripheral resistance. When the circumference of the arterioles decreases 12 per cent, the increase in the resistance in these vessels is as much as 50 per cent, leading, unless compensated, to a similar rise in blood pressure. Thus a change in circumference of the small peripheral vessels which on microscopic examination might easily be overlooked can have a profound influence on the blood pressure. The total peripheral resistance also depends on the number of open peripheral blood vessels, and it has recently been shown that their number is variable from moment to moment. Quantitative estimates of a large number of random regions are required before the total number of open vessels can be assertained, since casual inspection of a few random sections may fail to reveal the reduction of the total number of peripheral channels. In short, relatively small superficially unapparent changes in the tone of the smooth muscle of many peripheral vessels can readily bring about a sufficient increase in peripheral resistance to establish a maintained elevation of blood pressure.

Furthermore, rough calculations indicate that the total quantity of blood contained in the human systemic arterial tree is about 250 cc. or only four times the cardiac output per beat. This small blood content of the arterial tree facilitates elevation and maintenance of the blood pressure by small changes in peripheral resistance. However, to be effective the peripheral vascular narrowing in the systemic circuit must be universally distributed. Experiments have shown that ligation of various major branches of the aorta has little if any effect on the arterial blood pressure, except in the case of ligation of the common carotids, where blood pressure readjustments occur by means of the carotid sinus moderator mechanism. It would seem, then, that constriction of the smaller blood vessels in any one region is of little consequence on the blood pressure since blood vessels in other regions are opened wider. In fact, this is the mechanism by which blood redistribution to various regions in accordance with need is accomplished. If hypertension is to develop, the increase in peripheral resistance in the systemic circuit should be practically universal, but this, of course, does not preclude the likely possibility that the action is greatest in the splanchnic area. Since the blood flow in the extremities remains within the normal range in hypertension in man, the peripheral resistance in the extremities must increase in proportion to the elevation in blood pressure. This could not be the case if the vascular narrowing were not more or less equally distributed throughout the systemic vascular bed.

At some time in the course of hypertension, organic changes occur in various arterioles throughout the body. Obviously if this process were diffuse, an added load of peripheral resistance would be supplied which would raise the blood pressure still further. The available evidence indicates that this arteriolosclerosis is very patchy in distribution, particularly in the muscles and cutaneous regions, and suggests that it plays only a minor rôle. The vascular involvement of the kidney is an exception, since here the distribution of arteriolosclerosis is much more uniform and it may be the only site in which appreciable sclerotic changes are seen. The rôle of this renal arteriolosclerosis will be discussed later. The organic changes in the arterioles elsewhere in the body apparently occur only late in the course of essential hypertension, either coincidentally or as a result of the hypertension, and may be of possible importance in reducing the nutrition of the organs in the areas involved.

The Ways in Which the Vascular Narrowing Can Be Established: Granting that the fundamental basis of hypertension is a sustained peripheral vasoconstriction, the responsible mechanism must be sought in the various neural or humoral mechanisms known to control the caliber of the peripheral vessels. Hypertension will occur 1) when the ability of the moderator mechanism to cope with the strain placed on it is decreased, or 2) when an increase occurs in the strain on the moderator mechanism.

1) A Defective Moderator Mechanism: The first question to be answered is whether hypertension may be the result of an inefficient moderator mechanism. The possible causes for such an inefficiency might be a) an inherited weakness in certain human strains in the ability of the moderator mechanism to cope with the ordinary load placed upon it; b) disease of the moderator end organs and nerves, in particular arteriosclerosis of their supplying arteries, weakening the moderator mechanism by decreasing the number and effectiveness of its elements; c) loss of distensibility accompanying arteriosclerosis, making the moderator mechanism less responsive to a given blood pressure rise, since in the last analysis the end organs initiating the moderator reflex are stimulated by the distention of the vessel wall within which they lie and not directly by the endovascular pressure. A sustained hypertension can be produced in any one of these three ways, provided the process is sufficiently extensive to prevent compensation by other parts of the moderator mechanism.

While the evidence is incomplete regarding weakness of the moderator mechanism, that which is available at present makes it unlikely that its inherent or acquired weakness is the primary mechanism of hypertension. This does not exclude the likely possibility that such weakness may contribute in the later stages to sustain the hypertension. The causes of hypertension must therefore be sought rather in some excessive neurogenic or humoral strain upon this moderator mechanism.

2) Neurogenic Strains on the Moderator Mechanism: Neurogenic strains may result from any of three general processes: a) Excessive stimulation of the vasomotor apparatus by an abnormally large bombardment of impulses coming from any part of the sensorium, including the higher levels of the brain. b) Hyperactivity or hyperirritability of the central nervous centers regulating blood pressure, which may be brought about by an inherently low threshold of these centers or induced by disease, especially by disturbances of the local blood supply to these centers. Because of the complexity of the integration of

these nerve centers, this involvement must be fairly widespread to be effective. c) Hyperactivity of the effector mechanism, which may be general, or localized in the autonomic outflow path with its interpolated neurones, in the myoneural junctions, or in the smooth muscle of the peripheral blood vessel walls.

Unfortunately, we have no means of differentiating these types of neurogenic hyperactivity. Thus the cold pressor test cannot distinguish between these various elements of nervous control, even if it were established that this test is reliable.

Again, sympathetic denervation cannot answer the question of neurogenic overactivity since there is no available way to determine its effect on the blood flow through the splanchnic area. The argument has been advanced that the normal flow in the limb, despite the higher blood pressure, indicates hyperactivity of the peripheral effector mechanism either in the myoneural junction or the smooth musculature. The demonstration of hyperactivity of the peripheral effector mechanism of the arterioles in the extremities does not necessarily indicate that such hyperactivity is universal, particularly when we realize that the circulation through the extremities is highly specialized for the regulation of body temperature. Direct evidence of increased local arteriolar reactivity must be obtained in other areas such as the splanchnic before the theory that hypertension is due to overactivity of the arterioles can be accepted.

A survey of the evidence available on the hypothesis that essential hypertension is caused by extensive neurogenic overactivity shows it to be so incomplete that we are not in a position to decide whether such hyperactivity exists or where it may reside. It would be unwise to consider this phase of the problem settled even should we assume increased reactivity of the arterioles. *3) Strains on the Moderator Mechanism of Humoral Origin:* Overactivity of the arterioles need not be neurogenic, but could result from humoral stimulation. An analysis of the humoral mechanisms which might cause excessive strain on the moderator mechanism shows that the source of such humoral stimulation could be in a) an excessive production or more limited destruction of normal endocrine products, b) an excessive production or more limited destruction of some general metabolic by-product, or c) an excessive production or limited destruction of a by-product of some specific organ not generally recognized as an endocrine gland. In the foregoing analysis it has been assumed of course that these substances are pressor in character. A similar effect from these three sources might be brought about if the substances concerned were depressor in character and formed in less than normal quantities or destroyed excessively. In discussing such substances it is also necessary to know the point where the substance acts, whether upon the end organs or afferent elements, upon the vasomotor centers, the efferent autonomic neurones or the smooth muscle of the blood vessels themselves.

The transient hypertension observed commonly during puberty and during the menopause as well as the abnormal elevation of blood pressure in the latter half of pregnancy might be correlated with known disturbances in the ratio and quantity of the various products of a group of endocrine glands.

Hyperplasia or tumors of the adrenal cortex are often associated with clinical hypertension and, by contrast, atrophy or other destructive disease of the adrenal cortex are strikingly associated with hypotension. Here again the mechanism is unknown, although presumably humoral, and because of the low incidence the relation to "essen-

tial" hypertension is speculative. The rôle of the adrenal has been emphasized in connection with the renal mechansim which is to be discussed later. In view of the close embryological association of the two structures, it is tempting to consider the products of the adrenal and the kidney as having analogous or synergistic effects on the blood pressure. However, the actual evidence is still in its infancy. The rôle of the hypophysis in hypertension has been recently strengthened by Cushing's description of the syndrome of pituitary basophilism. It seems more logical to refer this syndrome to changes in the adrenal cortex than to the findings in the hypophysis. Whether the link between the two organs is by the adrenotropic hormone or by other means is not known. Also, in spite of the possible rôle of epinephrine and pitressin in the normal control of arteriolar tone, there is no evidence of a significant disturbance in these two hormones in clinical or experimental hypertension.

4) The Rôle of the Kidney in the Mechanism of Hypertension: The products of organs not specifically regarded as endocrine must be considered as possible factors in the sustained elevation of blood pressure. However, of all the organs investigated, the only one that demands serious attention in this connection is the kidney. It is interesting that from the start of our knowledge of kidney disease and of hypertension, clinicians and physiologists have been in accord in placing the mechanism of virtually all human hypertension in the kidney.

The clinical facts of hypertensive Bright's disease and the recent ingenious experiments of Goldblatt and of others who have confirmed his work point indisputably to a causal connection between impairment in renal blood supply and high blood pressure. Such impairment may result from the so-called degenerative vascular changes of age, from inflammatory disease of the kidney, from any constriction of the main renal arteries, probably from the secondary effects upon the renal circulation of obstruction in the lower urinary tract, or, experimentally, from the deliberate mechanical interference with the renal arterial circulation. If any such impairment occurs, chronic hypertension of varying degrees is known to follow. However, in the vast majority of patients in the early stages of "essential" hypertension, no one has yet demonstrated that any of these disturbances actually operate. Some investigators believe that arteriolosclerosis limited to the kidney is universal in "essential" hypertension and some have considered it the *cause* and not the *result* of hypertension. The failure of nearly all pathologists to demonstrate this process previously has been explained as due to a lack of diligence in searching for the arteriolar lesions. We must insist, however, that the burden of proof is still on the proponents of the theory that renal arteriolosclerosis in general precedes hypertension.

If we are to consider the kidney as the hub of hypertension, and if organic changes in the renal arterial system are not present early in "essential" hypertension, then functional renal vasoconstriction must be present. This in reality merely interposes the kidney as an intermediary in the process by which hypertension develops, but does not fill out the two important gaps in our knowledge; namely, 1) how the vasoconstriction in the kidney arises and 2) how it mediates the development of hypertension.

The causes of renal and general vasoconstriction may be considered under the same headings outlined in the first two parts of this section, and the gaps obviously remain just as great. The

demonstration of the central rôle of the kidney should not be mistaken as the solution of the ultimate mechanism of hypertension. One important by-product of the recent concentration on the rôle of the kidney has been the recognition of the human counterparts of experimental hypertension due to unilateral renal arterial constriction. Thus, removal of the diseased kidney in a few cases of unilateral pyelonephritis with hypertension and good renal function, has been followed by a return of the blood pressure to normal.

There is at present no way of demonstrating whether renal vasoconstriction is present early in hypertension, although the recent studies of kidney function suggest possible approaches. Certainly the beneficial effects alleged to follow surgical denervation of the splanchnic area cannot be used as evidence for a primary vasoconstriction in the kidney, since very few patients have been operated on sufficiently early in the disease, and a much larger vascular bed than a kidney is affected by these surgical procedures. Further studies along these lines are necessary.

At whatever stage the kidney is involved in "essential" hypertension, we must find the mechanism within the kidney responsible for its effect on blood pressure. While there is some evidence that afferent impulses from the kidney may reflexly produce hypertension, this process is apparently transitory and any persistent hypertension must be based on a humoral mechanism. This implies some change in the metabolism of the kidney which will release abnormal amounts of a normal or abnormal pressor substance, or remove more than the normal amounts of depressor substances, or lead to a disbalance between formation and destruction of such normal or abnormal pressor or depressor substances. Interference with the blood supply of the kidney apparently can initiate this metabolic disturbance, and from the experiments of Goldblatt it is obvious that even a unilateral renal "ischemia" is effective. The high oxygen consumption of the kidney, out of all proportion to its needs as an excretory organ, its tremendous blood flow which may reach a level of a quarter of the total of the systemic output per minute, and the known peculiar synthetic activities of the kidney which are independent of its excretory function, make it conceivable that a specialized metabolic mechanism may reside in the kidney to regulate its needs for blood by distant adjustments of blood pressure. This point of view would indicate that the substance responsible for hypertension is a normal regulator of the driving force to maintain an adequate blood flow and blood pressure within the kidney itself. It is quite possible, however, that the substance is an abnormal one occurring only when the kidney is "ischemic."

The only potent pressor material in the kidney known to physiologists is the renin described by Tigerstedt and Bergman many years ago. This extract has the peculiar property of producing general vasoconstriction of a rather persistent character without obvious toxic effects. It is also significant, if confirmed, that the concentration of renin in the kidney is increased when the renal arteries have been mechanically constricted sufficiently to produce hypertension. However, much more evidence is necessary before this relationship can be accepted as the mechanism in experimental or clinical hypertension. Certainly, studies on the action of renin on the rate of renal blood flow are essential.

It is evident that the central rôle of the kidney in hypertension has been well maintained throughout the period

of investigation of this field. Certain details have become considerably clarified as emphasis has been shifted from one point to another, but considerable study is still needed to solve this important problem.

Hypertension and the Modern Tempo of Living: Man, subjected to his external environment, must integrate his individual activity into the social struggle. His reaction to this struggle varies. Some individuals give up very soon and become tired. Others are aroused and perhaps struggle excessively. The geographic and racial analysis of the distribution of hypertension, insofar as it has been studied by serious students, would make it seem that the highest known incidence of high blood pressure is among those who, exposed to the complexity of civilization, struggle against its restraints. Thus, in the aboriginal native protected against social struggle by collective emotional regulations, taboos, and ceremonies, the incidence of hypertension appears to be low. On the other hand, in the urban American Negro, who has been removed for several generations from his protective aboriginal society and placed in the civilization of the west, the incidence is high. This seems to be true also of the recently westernized Japanese, who now appear to have a high incidence of hypertension as compared with the presumably similar stock, the Chinese, who have not yet succumbed to the intricacies of Western civilization but have retained the calm state of mind which distinguishes their attitude toward life. It is only fair to state that the documentary evidence upon which these statements are based is fragmentary and inadequately controlled. This field of study evidently demands intensive pursuit because of its fundamental bearing on the problem of hypertension as a disease of civilization. An opportunity exists in this country of studying the Negro from this point of view, in industrial communities, on the plantations and in the all-Negro communities of the South, and the islands adjacent to our continent.

Even though it is difficult at present to establish definitely the relationship between civilization and hypertension, it is permissible, we believe, to speculate on the possible factors in civilization which should be more thoroughly investigated. Superficially, it appears that the factor is not diet nor the excessive use of tobacco, alcohol, and cerebral stimulants, although these cannot, in our present state of knowledge, be entirely ruled out. Likewise, climate, clothing and housing are not the primary variables involved, although here also the evidence is not final. More significant, probably, is the effect of Western civilization upon the mental conflicts of man. This is a field which the psychiatrists have barely touched. Intensive controlled investigations of this subject will repay the effort involved, and may make the contribution of the psychiatrist of the utmost importance in the general problem of hypertension.

In pursuing such studies, the psychiatrist should attempt to convert his data into terms of physiology and biochemistry just as the experimentalist in medicine and physiology attempts to convert his data into terms of physics and chemistry. At present much of the language of the psychiatrist is so far removed from that of the other medical investigators that his work is not subjected to the beneficial mutual critique which students in different fields exert upon one another.

In this connection, it may be justifiable to digress along metaphysical lines to show that mental activities have not yet been brought into a line

with the view that all nerve activity is a form of physical energy. The body, after all, is in contact with its external and internal environment insofar as various forms of energy operate upon the sensory end organs. Changes in the energy content of the environment act as the stimuli to the sense organs, establishing in them another form of energy, the exact nature of which is unknown. The energy liberated in the end organs serves as the foundation of the series of nerve impulses, another form of energy, that travel up the nerves at various rates and from various regions to summate in the nerve centers which discharge another form of energy that initiates impulses to the effector organs.

From this point of view, mental activities must be considered as a peculiar and imperfectly understood manifestation of energy occurring in the highest nerve centers as a result of energy released by stimulation in the sense organ periphery. Mental processes, we believe, may be conceived as a manifestation of some more fundamental energetic process inadequately described by the psychiatric terminology, rather than as a form of energy which can, *per se*, initiate nerve impulses to control blood pressure. This does not in any way impair the purely descriptive aspects which psychiatrists have pursued in correlating blood pressure changes with mental processes, but shows that a link is still missing in the chain between the volitional and emotional aspects of life and their somatic representations. To repeat, the point we wish to make is that the coincidental finding of somatic reactions and psychiatric manifestations does not establish that the latter is the direct cause of the former, because the two are at present still in totally different realms of knowledge. It is much easier to conceive that somatic reactions through the operation of somatic sense organs can result in changes in the higher centers which can give rise to psychic accompaniments.

Conclusion

In this presentation we have attempted to review briefly the known physiological facts in the control of blood pressure and to describe the major aspects of the clinical picture of "essential" hypertension. On the basis of the physiological and clinical material discussed, we have tried to outline the probable factors underlying the disturbance in the regulation of blood pressure which leads to high blood pressure. It must have become obvious to the reader that numerous and varied approaches to the problem of hypertension have been made and are still necessary for its solution. Not the least of these is the psychosomatic study of man in relation to his environment—internal and external alike. In this realm psychiatrists should play a leading rôle, because it is to them that we must turn for our knowledge of the analysis of modern civilization, in which the hypertensive state seems to flourish. Direct cooperation between psychiatrists and other medical investigators, and direct coordination of psychiatric studies with other medical investigation, are obviously needed in this field, more perhaps than in any other.

PSYCHOSOMATIC MEDICINE—VOL. I, NO. 1, JANUARY, 1939

SYMPOSIUM ON HYPERTENSION

BLOOD PRESSURE AND PALMAR SWEAT (GALVANIC) RESPONSES OF PSYCHOTIC PATIENTS BEFORE AND AFTER INSULIN AND METRAZOL THERAPY

A PHYSIOLOGIC STUDY OF "RESISTANT" AND COOPERATIVE ATTITUDES*

ALFRED P. SOLOMON, M.D., CHESTER W. DARROW, PH.D., AND MELVIN BLAUROCK, M.D.**

THE RECENT advent of pharmacologic treatment of the psychoses has provided an unprecedented opportunity for securing physiologic data on the same patients before, during and after remission or recovery. We present here results on patients from the University of Illinois Psychiatric Institute who have been studied in the psychophysiological laboratory of the Illinois Institute for Juvenile Research.

Psychologic Resistance and Cooperation: In this paper we report certain autonomic reactions to ideational stimuli which, along with changes in the patient's attitudes, tend to be changed following pharmacologic treatment. The attitudes with which we are concerned are those which may be referred to as psychologic "resistance" on the one hand and as ready cooperation on the other hand. In one of our groups of cases the psychologic resistance was manifested as hostile, angry, disputing attitudes toward the examiner. In another group it was evident as perplexity and confusion incidental to the discussion of personality problems. In the latter group the perplexity and confusion of the patients was generally related to the consideration or discussion of their hostile attitudes toward members of their families, and to their ambivalent attitudes toward other apparently repressed ideational material. The patients were rated as resistant or cooperative primarily on the basis of their overt behavior, including the nature of their verbal responses at the time of the test. Observations of behavior on the ward were given full consideration.

Physiologic Measures: Simultaneous blood pressure and palmar galvanic responses to sensory, indifferent ideational, and crucial ideational stimuli presented by the psychiatrist have been analyzed for the present study. Blood pressure has been recorded both by the sphygmomanometric continuous method (*13*, *16*) and (in the more recent of the cases) by a new method continuously recording systolic blood pressure

* Studies from the Psychiatric Institute of the University of Illinois and State Department of Public Welfare and from the Institute for Juvenile Research, Series C No. 288. Presented June 9, 1938 before the American Psychiatric Association in San Francisco. The study included two cases treated by Dauerschlaf.

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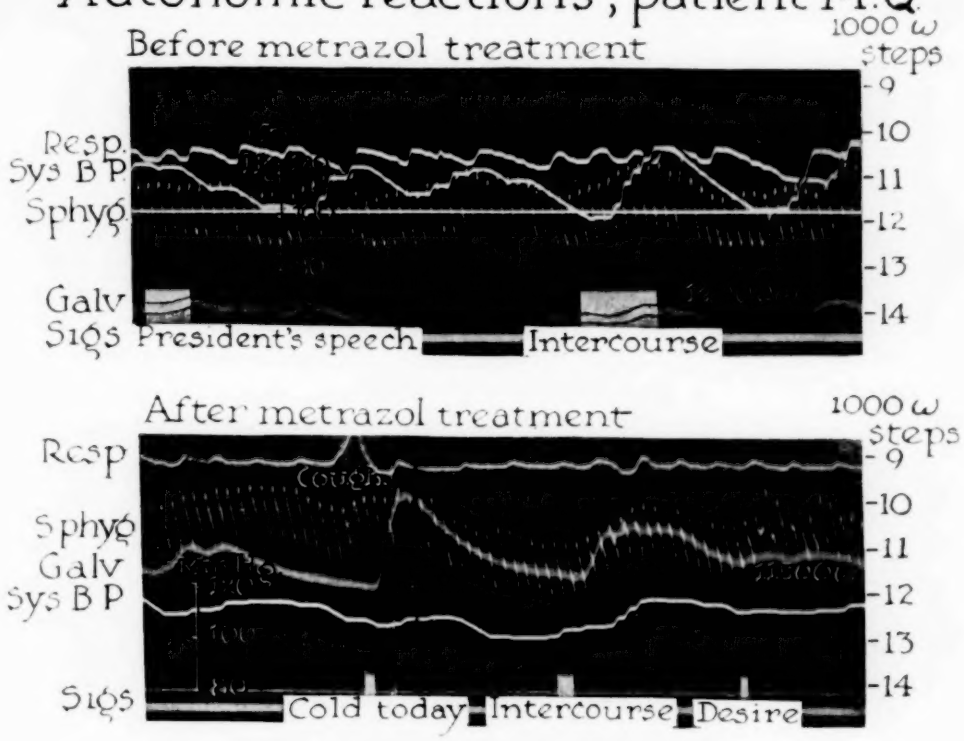


FIG. 1. Autonomic Reactions of Patient M.Q.

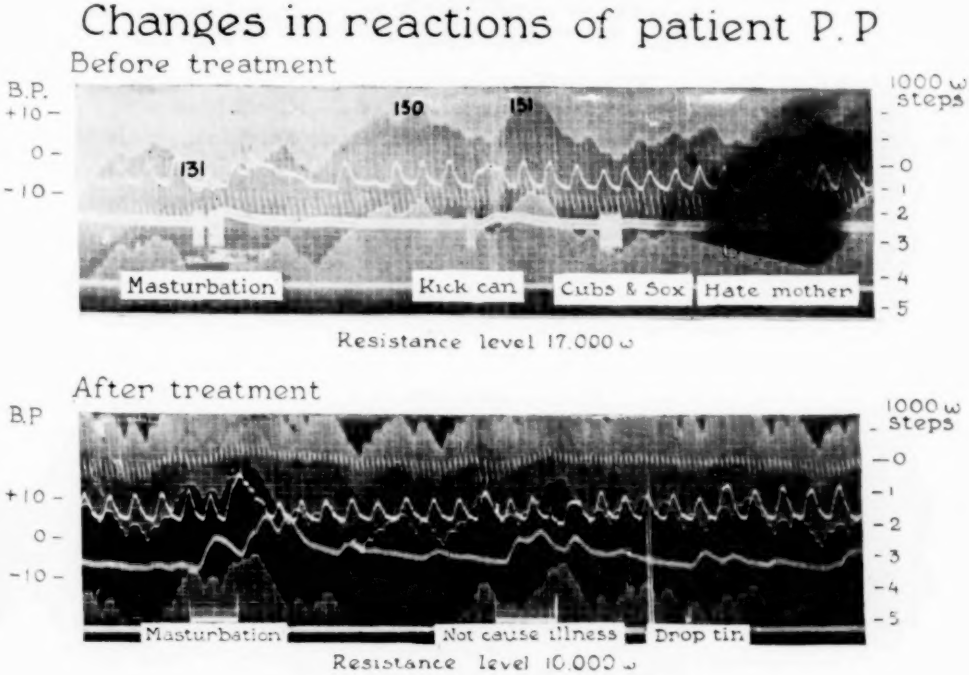


FIG. 2. Autonomic Reactions of Patient P.P.

In Figs. 1 and 2 the curve, Resp., represents respiration; Sys. B.P. is a continuous record of systolic blood pressure obtained by our continuous recording apparatus: Sphyg. is a continuous B.P. record by a sphygmomanometer, Galv. is the continuous quantitative record of the palmar galvanic skin reflex (palmer sweat reactions) and Sigs. are signal marks. The vertical white lines are second marks. In Fig. 1. B.P. is recorded by mercury manometer, ½ mm.=1 mm. Hg change. In Fig. 2, B.P. is recorded by the edges of semitransparent vanes on a Tycos dial manometer, 1 mm.=1 mm. Hg change.

(*15*).[1] The systolic record has commonly been recorded from one ankle with the patient reclining and the sphygmomanometric record taken from the other ankle. The simultaneous recording of relative sphygmomanometric pressure and of systolic pressure from the same patients has provided a means for translating sphygmomanometric readings into approximations of readings in mm. Hg change in cases where the systolic records are lacking.

Galvanic measurements of palmar skin resistance have been recorded by a continuous method automatically keeping current constant (*20*). Electrodes were relatively nonpolarizing, of physiologic $ZnSO_4$—kaolin paste on Zn. They were of "table type" supported outside the area of electrical contact (*17*).[2] Recorded resistance changes have been translated into *Log conductance change* because conductance provides a measure of the amount of physiologic activity (sweating) (*19*),[3] and because the logarithm of the physiologic activity appears to correspond with variations in the psychologic response. Inspection of our data indicates that the success of the galvanic measures in differentiating the status of our patients before and after recovery depends to no small extent upon the use of log conductance as the unit of measurement.

Recorded Physiologic Reactions: The change in physiologic reactions before and after pharmacologic shock treatment is illustrated by the sample records of Figs. 1 and 2.

In the upper record of Fig. 1 obtained before treatment the patient was hostile to questioning regarding her frankly ambivalent attitudes about sex. The record shown below was taken later when she has recovered and was exhibiting a cooperative cordial attitude toward the examiner with an objective outlook and an apparently adequate rationalization of her problem. It will be noted that before treatment the record shows very slight galvanic reactions whereas after treatment the reactivity is greatly increased. The systolic blood pressure response appears in this case to be somewhat reduced following treatment although the mean level of pressure remained around 110 mm. (Hg in both instances).

This same general change in the pattern of physiologic reactivity is illustrated in another case (Fig. 2). It is again to be noted that the galvanic reactivity to a crucial question regarding masturbation is greatly increased following recovery and the blood pressure response is somewhat reduced, although the mean level of systolic pressure is around 140 mm. (Hg in both records). Responses of this patient to other stimuli before and after recovery are graphically presented in Fig. 3.

The Autonomogram: The changes in galvanic and blood-pressure reactivity following various types of stimuli (crucial ideational, indifferent ideational

[1] Our sphygmomanometer records have all been obtained at a pressure between systolic and diastolic levels since a sphygmomanometer record obtained at less than diastolic level provides *not* a blood pressure but a plethysmographic record complicated by blood pressure. This is important since below diastolic level, blood pressure and plethysmographic changes occur in opposite phase and tend to counteract each other.

[2] Description of electrode reference (*17*) p. 292.

[3] A basic non-variable resistance of 3,000 ohms has been assumed in the cases of all measurements and subtracted from the measured resistance before calculating log conductance. This is recognized as only a partial correction, but in the absence of an adequate measure of non-variable resistance it is less likely to give rise to distortion of results than a larger correction. It is obvious that this correction becomes significant only at low resistance. Log conductance values have been multiplied by 100 for convenience in manipulation. Calculation is as follows:

$$\text{"Log cond. change"} = 100 \log \frac{1}{\text{res}_2 \text{ in megohms}} - 100 \log \frac{1}{\text{res}_1 \text{ in megohms}}.$$

Cf. short cut in use of slide rule for calculating log conductance, reference (17), p. 290.

and sensory stimuli) by individual patients have, for convenience in interpretation, been plotted on two dimensional graphs, called autonomograms (*12*) with blood pressure change represented along the ordinate and galvanic response along the abscissa.

The grouping of the galvanic responses in the autonomogram into "class intervals" termed zero, small, medium, large, and extreme, and the blood pressure reactions into class intervals designated +++, ++, +, o, −, −− permits convenient graphic representation of each patient's reaction-picture by words or phrases representing the various stimuli typed into appropriate rectangles in the autonomogram.

The division points for the "class intervals" at which the lines are drawn to form the rectangles of the autonomogram were originally determined by subdividing the reactions of groups of subjects on which we had distributions of reaction measurements. The original divisions thus determined have been slightly modified to provide the easily remembered division units involving multiples of 3 as follows (Table I):

TABLE I

B.P. Measures along the ordinate of autonomogram		
Designation	Numerical value of class interval	mm. Hg change
+++	3	27 & over
++	2	9 to 27
+	1	3 to 9
o	0	−2 to +3
−	−1	−6 to −2
−−	−2	less than −6

Galvanic Measures along the abscissa of autonomogram		
		Log conductance change
Extreme	4	over 18
Large	3	6 to 18
Medium	2	2 to 6
Small	1	0 to 2
Zero	0	0

Figs. 3A and B show the general character of the reactions of a patient plotted in this manner before and after recovery. The autonomogram 3A on the left shows the reactions before metrazol treatment and 3B on the right shows the reactions of the same patient to similar questions after treatment. The reactions to crucial ideational stimuli, which have been bracketed with heavy lines are seen to have shifted toward the right and center of the autonomogram, indicating increased galvanic and unchanged blood-pressure responses to crucial items. The following protocols present a stenographic report of crucial questions and answers referred to by the numbered items in autonomograms 3A and 3B.

Stenographer's Report of Test on Pt. P.P.

A. BEFORE TREATMENT

(Numbers correspond to items in Autonomograms Fig. 3A and 3B.)

A test of reaction to threats, conditioning, reactivity, adaptation etc. to repeated sensory stimuli (auto horns) precedes the reactions to mixed sensory, indifferent ideational, and crucial ideational stimuli. The crucial ideational stimuli were the following:

2. Why did you use an assumed name?
   Why? Through adoption or something.
5. Have you ever had sexual intercourse with a girl?
   Yes—moves left hand.
6. Did you love this girl?
   No.
9. Are you worried about the fact that you masturbated—that you played with your penis?
   Yes.
10. Is that the reason you are a patient here?
    Yes.
11. How frequently did you masturbate?
    Quite a good deal.
13. What about your mother, do you love her?
    Mother—no.

BEFORE TREATMENT

Confused; poverty of association, frankly expressed resentment of family, frequent absence of response.
Log Conductance Level 195 to 185

Patient P. P.
Test I.

LOG CONDUCTANCE CHANGE

B. P. 138/93	Zero	Small	Medium	Large	Extreme
+++		16.Masturbation 19.Hate mother	} Crucial ideational	stimuli	
++		17.Kick can 24.Warm here Pimples 20.Tell about mother 21.Ashamed of mother 31.Love father 32.Why hate father 38.Reason hate father 39.Mother do something to you 40.Why hate her 41.Want her to love you 43.Care of face 44.Fruit peddler 47.Eine boy not worry mastur.	Clap hands 25.Gong } Indifferent Warn questions Crucial ideational stimuli	Horn 1 } Sensory stimuli 21.Threat pin	
+		22.Ashamed talk that way 28.Girl a prostitute 33.Who represent Rained today 46.Shoes shined Horn 3 Sneeze 14.Clap hands	Warn horn Indifferent ideational stimuli Horn 2	Sensory stimuli	
0		12.Shout 42.Squawk 45.Gong 30.Summer 34.Allah who had garden?			
-		1.Comfortable 23.Gong			
--		Poor in Science			

FIG. 3A

Patient appears to have a confused expression, occasionally wrinkles his brow and wipes it with his free hand, sighing.

16. What is the reason you masturbated so much when you thought it would hurt you?
Well to keep from eating so much.

19. Why do you hate your mother so much?
I hate her—because—I know her history, I know what it is.

20. Tell me more about it.
Well she went to public school.

21. Are you ashamed of your mother?
Yes.

22. Aren't you ashamed of yourself talking that way?
Yes.

31. Do you love your father?
No.

32. Tell me why you hate your father?
I know who he represents.

33. Who does he represent?

RECOVERED FOLLOWING METRAZOL THERAPY

Comes gladly to test expressing gratitude for recovery; exuberant over new job.
Log Conductance Level 222

Patient P. P.
Test IV.

LOG CONDUCTANCE CHANGE

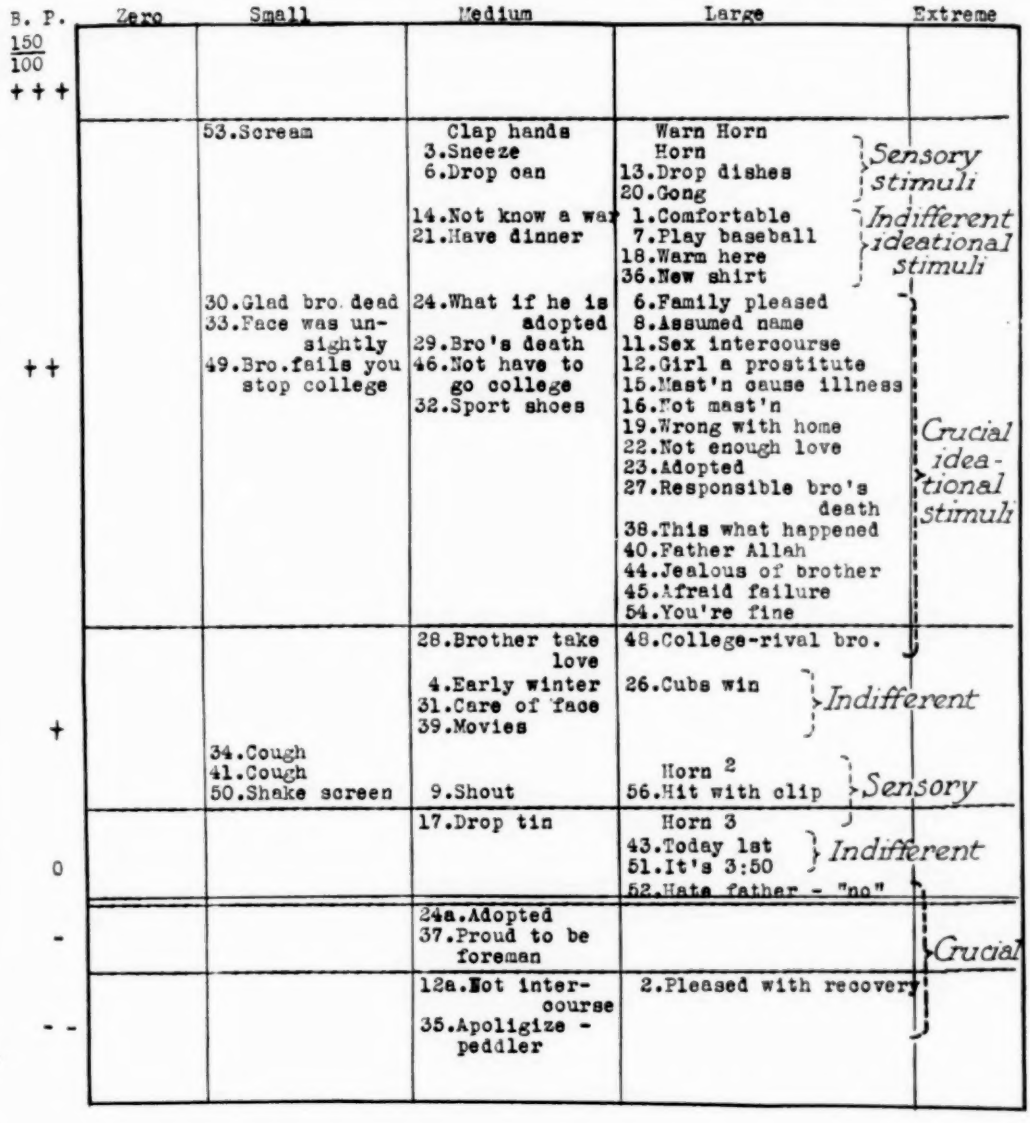


FIG. 3B

Allah.

34. Do you mean the Allah that has a garden?
Mm—Yes.

38. What is the reason you hate your father, when you say you hate him because he is Allah?
He doesn't give me any consideration—I fear seeing him.

39. Does mother do the same to you?
No.

40. Why hate her?
She doesn't like me.

41. Do you want her to love you more?

That is part of it.

43. I should think you would take better care of your face—it is rather unsightly.
No answer.

44. Did you tell me that you were a fruit peddler?
Yes.
Reassurance:
You have passed a satisfactory test. You will come later to understand more about your problems.

B. AFTER TREATMENT WITH METRAZOL

Patient returned to hospital for the test by special appointment. He was employed at the time as a skilled workman in a factory manufacturing automotive specialties. The initial test of reaction to threats, conditioning, reactivity, adaptation etc. to repeated sensory stimuli (auto horns) precedes the reactions to mixed sensory, indifferent ideational, and crucial ideational stimuli. The following were the crucial ideational stimuli.

2. I cannot tell you how pleased I am that you have recovered. It is really gratifying to us.
Appreciative answer.

5. I imagine your family was pleased to have you at their wedding anniversary dinner.
Yes they were (broad grin).

8. Why did you think you had an assumed name?
That's all foolishness—I have forgotten all about that.

11. Did you have sexual intercourse with that girl that you talked about?
Does not appear to understand question.

12. Was she a prostitute?
Confused about question. Finally denied that he had had coitus.

12a. Then you didn't have intercourse with a girl?
One.

15. You used to think that masturbation caused your illness.
Not so much, it might have had something to do with it.

16. I want you to know that it was not masturbation, but your guilty feelings about it.

19. What was wrong with your home life?
Nothing really—I was pressed for money when going to school.

22. Did you mean that you were not given enough love by your family?
Not so much that—I don't expect that now.

23. What is this mystery in your family that you talked about when you were sick?
Just that father was adopted—I did not know it till grandfather died. It bothered me that his name was changed—got on my nerves. That is why I thought I had an assumed name.

24. What difference does it make if he was adopted?
That is why I thought I had an assumed name.

24a. What made you think you were adopted?
I felt that way as a child; the kids taunted me about it.

27. Do you feel you are responsible for the death of your brother?
No.

28. Did you feel the baby would take some of the love belonging to you?
No—he didn't live long enough.

29. What did you think of his death?
He died in the hospital—I didn't go to the funeral and didn't know much about it.

30. As a little child did you feel glad he didn't live—Not take away any of your love?
No—It was God's will.

31. You took my advice and took care of your face—I notice it is clearing up.
Yes I did.

33. Your face did look unsightly.
Sure.

35. Why did you feel so ashamed or apologetic about your job as a peddler?
I did at the time I felt my chances were poor—made me feel low down. I didn't like to take nagging from the neighbors, and customers made me feel bad.

37. You are proud of the fact you have worked up to foreman so soon?

Yes I am.

38. Now as I understand, this is what happened. As a child you learned that your father was adopted and subsequently you worried about yourself being adopted and not being sufficiently loved.

40. Why did you call your father Allah?
I was mixed up.

44. Are you jealous of your brother's proficiency?
Not so much, though to a certain extent; I worried more that he did not get a better position.

45. Were you afraid you might be a failure like your brother?
If that was all I could get out of college, it was not worth it.

46. But was it true you didn't have to go through college when your brother didn't succeed?

47. You went to college to compete with him?
Yes.

49. So when he didn't make good you didn't have to struggle to get through?

51. Do you still hate your father?
No.

Reactions of a Group of Overtly Resistant Hostile Patients: A summary of the reactions of a group of five overtly resistant hostile patients to the crucial ideational stimuli is shown in Fig. 4. The patients in this group were classed as resistant because before treatment they did not present a cooperative attitude which permitted a frank discussion of their emotional problems, but instead they exhibited an antagonistic, hostile resentful attitude toward the examiner. Changes in blood pressure in response to the stimuli are here plotted in the class intervals or squares along the ordinate and changes in galvanic activity have been grouped in the class intervals along the abscissa. The reactions before and after treatment, represented respectively by the circles and the crosses, have been arbitrarily grouped within the respective squares to assist visual interpretation. It is to be noted that before treatment the reactions represented by circles tend to fall toward the upper left portion of the autonomogram, whereas the reactions following recovery, represented by the crosses, tend to fall toward the upper right-hand corner and the middle right hand portion of the graph. The average of blood pressure reactions in this group

PSYCHOLOGIC RESISTANCE WITH OVERT HOSTILITY; IMPROVEMENT FOLLOWING TREATMENT

Reactions to Crucial Ideational Stimuli
O = Reactions of five cases during psychosis
X = Reactions after remission of symptoms in four and improvement in one of these cases

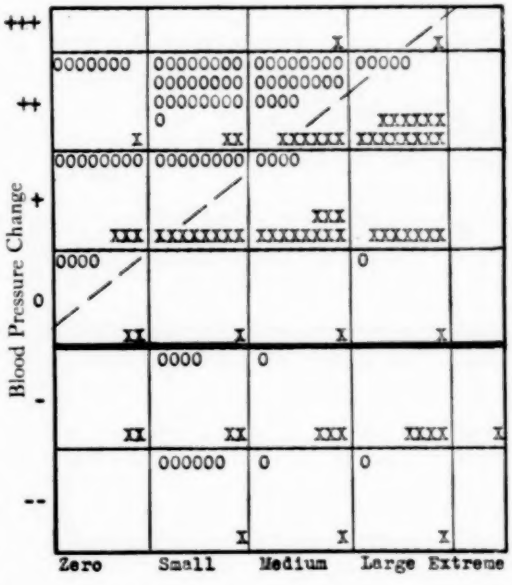


FIG. 4

showed evidence of only a slight reduction in magnitude and the level of systolic blood pressure was not appreciably altered as the result of treatment. The blood pressures of these patients at the time of the test were respectively 110/80, 160/90, 114/90, 120/80 before treatment, and 106/80, 166/80, 130/90, and 122/82 after treatment. In one case systolic pressure at the time of the test before treatment

was not available; after treatment it was 110/80. The respective ages of these patients was 36, 20, 26, and 27, and in the latter instance, 29.

The nature of the questions asked this group of patients and the general character of their reaction to the tests before and after treatment are indicated by the following illustrative summaries:

Pt. M. Q. female, age 36. An excerpt from this patient's physiologic record is presented in Fig. 2. Crucial questions based on material in the case history were related to sex traumata in childhood, severe emotional conflict regarding sex in young adulthood, flight into a very strict convent, and rebellion against ritualistic restrictions which finally precipitated a psychosis characterized by rebellious attitudes and behavior indicative of a great but unadmitted interest in sex. Questions regarding her exhibitionistic and seductive behavior were met by emphatic denials, forceful assertions, evasive rationalizations, some reluctant admissions, and energetic self-reassurance. Following treatment with metrazol and apparent recovery the patient was cooperative, cordial, had insight into her sexual problems, and made frank admissions accompanied by blushes concerning previous overt sex behavior. An example of her response to questioning is as follows: On the first test: "Don't you find that your shapely legs get you into trouble sometimes?" Ans. "What do you mean getting me into trouble? No never, it is just a pair of legs to walk on. Anything that goes around sopping up legs they certainly couldn't be a very interesting companion. However, there has been a lot of attractions for those legs, but it wasn't on my part." On the second test: "Do you still have trouble with men looking at your legs when climbing up on street cars?" "I don't seem to notice it and I don't think legs are the problem they used to be with short dresses." Blood pressure at time of test before treatment, 110/80; after treatment, 106/80.

Pt. D. L. male, age 29. Crucial questions were selected from material in the case history relating to excessively dependent attitudes toward mother and wife, a fixed idea that he had killed his father in an assault during the psychosis, and feelings of self-depreciation and self-condemnation related to inadequate masculine adjustment leading to economic and marital failure; somatic delusions. During the first test he was bitter and surly. When confronted with a strong persuasive statement that his father was alive he avoided an admission in an argumentative manner. Questions related to his prepsychotic maladjustment provoked emphatic self-depreciatory replies. Reassurance brought sarcastic comment. On the later test the patient was about to be discharged as recovered. He had given up his feelings of self-condemnation and self-reproach. Attitudes of resentment toward his father were not present. He showed realistic attitudes toward his wife and children. He cooperated well. Blood pressure on test after treatment 110/80.

Pt. E. L. male, age 20. The crucial questions were selected from material in the case history relating to his love for his mother and hostility toward his father and to a desire for artistic intellectual superiority expressed as an omnipotent, critical, sneering, superior attitude toward his father and society, a maladjustment which resulted in the psychosis, when he amputated his finger while working as a laborer in a steel mill. During the first test the acute phase of his psychosis had already subsided. He was in good contact with the test situation. He was hypercritical of the examiner's choice of words, correcting the terminology of the questions in a pedantic manner. He rejected opportunity for discussion of his problems preferring to exhibit evidence of his linguistic superiority. In the test preceding his discharge from the hospital as recovered, he answered all of the questions in a deliberate manner still making an exaggerated attempt to be accurate. Compulsive ideas of superiority did not appear in his responses. He was cordially cooperative. Examples of his quibbling which were present on the first test but not on the second test were the items: "Roosevelt has been nominated by the Demo-

cratic Party". Ans.: "Renominated you mean". "Governor Horner will probably win again". Ans.: "Win; is that the way it is—I thought it was the public's choice." "My former impression of you was that you were always well groomed and a gentleman." Ans.: "Maybe not well groomed, but a gentleman." Blood pressure on test before treatment, 114/90; after treatment 130/90.

Perplexed Confused Group: The reactions to crucial ideational stimuli by a group of seven patients selected because of confusion and perplexity regarding their problems, or refusal to discuss them, is presented by autonomogram in Fig. 4. The individuals in this group exhibited at the onset of the psychosis impulsive aggressive acts and demanding attitudes toward members of their families, which did not exist in the prepsychotic state. During the test, questions relating to this behavior provoked replies indicating considerable perplexity. This evident confusion was, therefore, regarded by us as a form of psychologic resistance to the consideration of their problems. The verbal responses of these patients after treatment, confirmed the interpretation that unexpressed hostilities and other conflicts had existed prior to the psychotic episode during which this confusion provided indication of resistance to their discussion. It should be indicated that these patients did not exhibit the type of confusion or amentia seen in the toxic psychoses. In this group we see the reactions to crucial questions before treatment—large rise in blood pressure and small galvanic response—as indicated by circles in the upper left portion of the autonomogram. After treatment, with the disappearance of the above described perplexity the reactions to the same type of stimuli are characterized by large galvanic changes and are indicated by the crosses at the upper right and middle right portion of the graph. The average of blood pressure responses was slightly increased, but as in the preceding group the *level* of systolic blood pressure was not materially changed by treatment. The respective systolic blood pressures of individuals in this group before treatment were 138/93, 106/80, 118/88, 124/84, 110/98, 122/80,

PSYCHOLOGIC RESISTANCE CHARACTERIZED BY CONFUSION; IMPROVEMENT FOLLOWING TREATMENT

Reactions to Crucial Ideational Stimuli
O = Reaction of seven patients before treatment
X = Reactions of same patients following treatment and improvement

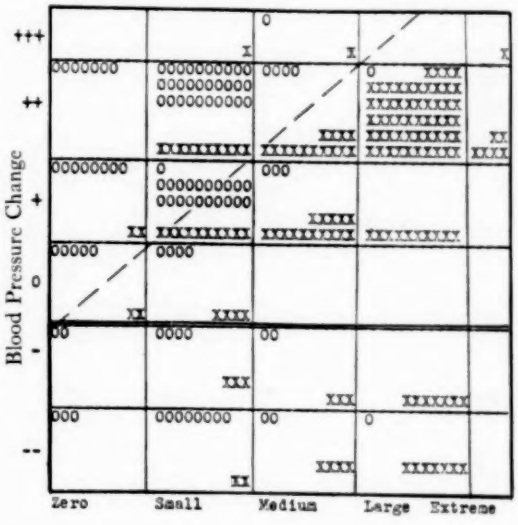


FIG. 5

and 128/80; after treatment they were 150/100, 100/84, 115/85, 124/60, 109/74, 120/80, and 118/80. The ages were respectively 20, 15, 31, 15, 20, 18, 38. The nature of the stimuli and general character of the response of this group of patients to the test situation are indicated by the illustrative summaries.

Illustrative Summaries, resistant perplexed patients:

Pt. P. P., male, age 20. This case has been

presented in detail by a sample physiologic record before and after treatment, Fig. 1, and by the autonomograms and protocols of Fig. 3A and B. The crucial questions were taken from material in the case history and related to feelings of rejection in childhood, guilt about an infant brother's death when patient was age five, a fixed idea in childhood that he was adopted, manifested in the psychosis as a delusion that he had an assumed name, and a feeling of inadequacy about his social adjustment, and, later during the psychosis, an overtly expressed hostility toward his parents and twin brother. The first test was characterized by marked perplexity over his frankly expressed conflictual and confusional ideas. During the later test subsequent to insulin followed by metrazol treatment, when he had clinically recovered and had secured a job, his replies indicated rather good insight into the conflicts and the episodes of the psychosis. He was extremely cordial, grateful, and cooperative. Blood pressure before treatment was 138/93, after treatment 150/100.

Pt. A. C., male, age 15. Crucial questions were selected from the material in the case history and related to his conflict about playing a more mature rôle in his home following the homicidal death of his father, his impulsive aggressive acts during the psychosis, his perplexity about the reasons for the murder of his father and grandfather. During the first test he was frightened and confused. To many of the questions he muttered an unintelligible answer. To the others he indicated he was puzzled and undecided. On the later test he was not confused, gave relevant and appropriate answers. He had some insight into the conflict between his desire to play a manly rôle in the home and his previous excessive dependence on his mother. Blood pressure before treatment was 106/80, after treatment 100/84.

A comparison of the reactions of the resistant hostile patients with those of resistant confused patients shows that the physiologic mechanisms involved are in general the same as far as our records are concerned, and that essentially the same alteration in response is induced by satisfactory pharmacologic treatment in the two groups. We have, therefore, combined the data of the two groups of patients for statistical treatment.

It is further evident from examination of Figs. 4 and 5 that a better differentiation of clinically recovered from unrecovered patients occurs in the case of reactions involving a rise than when there is a drop in blood pressure. The negative blood pressure reactions have, therefore, been omitted in the statistical summary of the reactions of resistant patients before and after successful treatment presented in Table II.

TABLE II

GALVANIC AND POSITIVE BLOOD PRESSURE RESPONSES OF RESISTANT PATIENTS BEFORE AND AFTER SUCCESSFUL PHARMACOLOGIC TREATMENT

(Data represent the numerical values of class intervals or fractions of intervals as defined in Table I and illustrated in Fig. 6.)

	Number of Reactions	Blood Pressure Change	Galvanic Response
Before Treatment	165	1.53±1.10	1.03±0.86
After Treatment	191	1.56±1.19	2.22±1.56
Difference		0.03±0.12	1.19±0.13
Crit. Ratio Dif./PE dif.		0.24	9.15
Chances in 100 of a true dif. greater than zero		50	100

Several factors may contribute to the poor differentiation characterizing the minus changes. 1) Minus blood-pressure changes may be read from the record with less certainty than the positive reactions: they are smaller and it is often difficult to differentiate a minus response to stimulation from a recovery after a preceding rise. 2) Vasoconstriction as a result of stimulation may have contributed to minus changes in those records where we

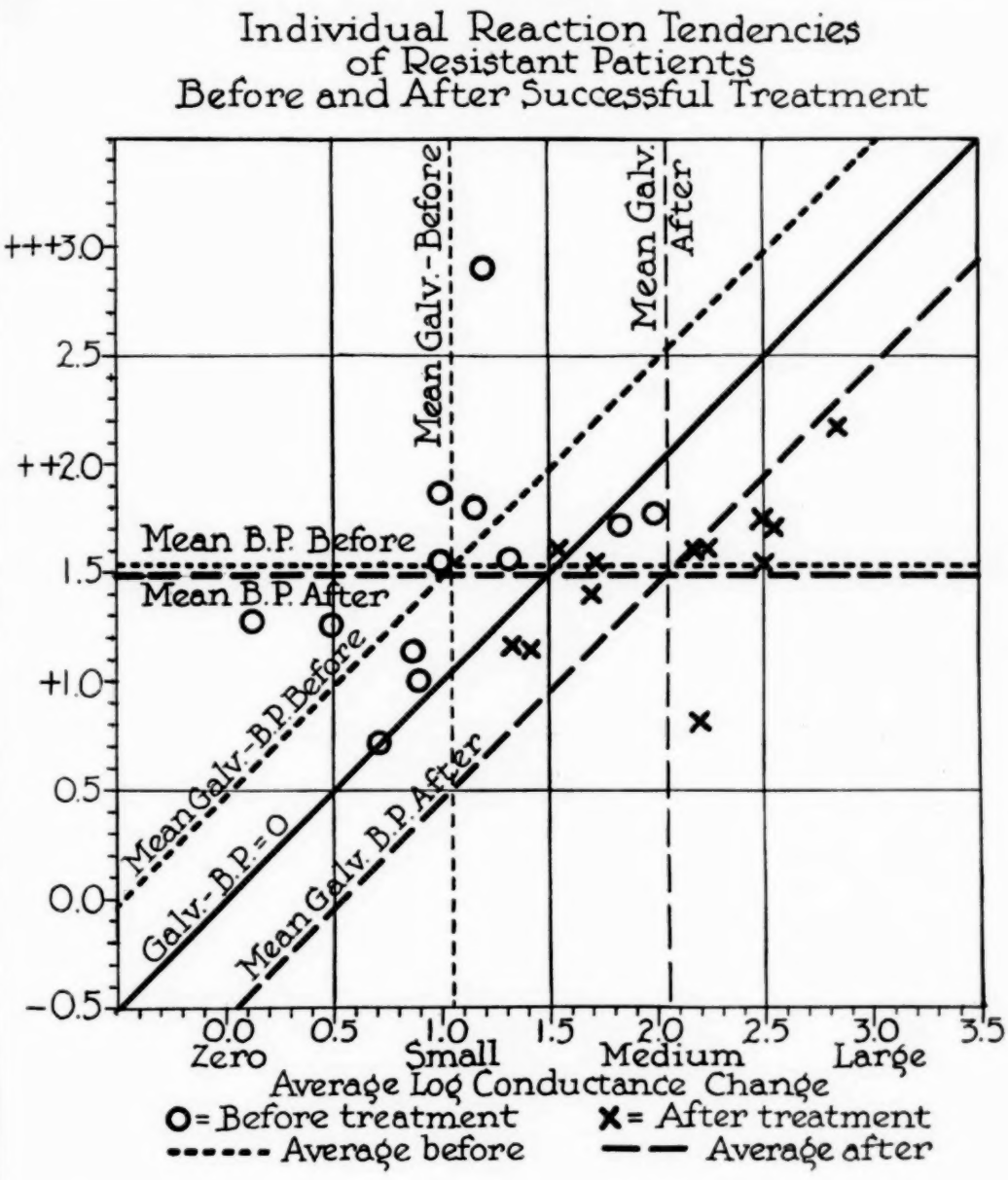


FIG. 6

depended solely upon the sphygmomanometric record.[4] 3) Physiologic influences such as adrenergic vasodilatation give ambiguity to the interpretation of the minus changes more than is the case with positive responses. We have therefore confined our present consideration largely to reactions involving positive blood pressure change—those above the double line in the autonomograms.

It is apparent that the change with treatment is primarily in the magnitude of the galvanic response. This is true notwithstanding the fact that the mean positive blood pressure response within the autonomogram was slightly though not significantly reduced following treatment in the resistant hostile group and slightly in-

[4] *Cf.* fn. 3 p. 120.

creased in the resistant group. Since, however, both blood pressure and galvanic autonomic effects are simultaneously obtained it is clear that it is not the blood pressure reaction alone nor the galvanic reaction alone but the change in the galvanic response *relative to* the practically unchanged blood pressure reaction which requires explanation.

The Individual Reaction Tendencies: The averages of positive blood pressure

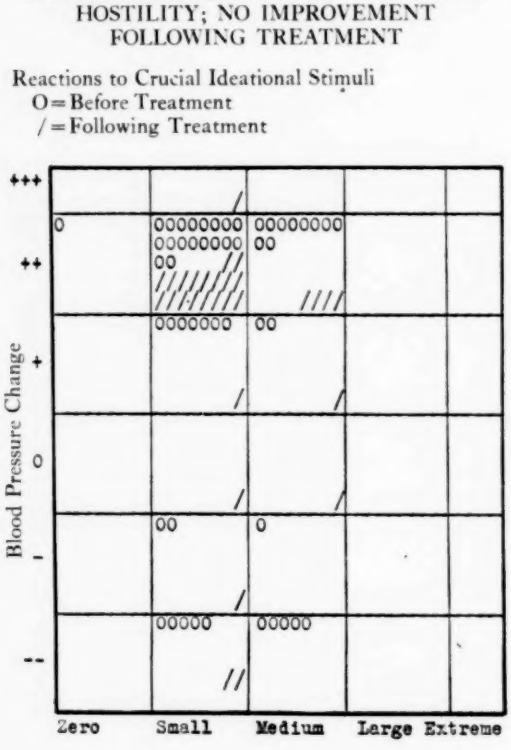


FIG. 7

reactions and of galvanic responses before and after recovery have been determined for each of the individuals whose responses are given in Figs. 4 and 5, and the results have been plotted in Fig. 6. It is here again evident that it is the relation of the galvanic to the blood pressure response which is significant. It is apparent from inspection that a diagonal line which represents the difference, galvanic-minus-blood-pressure response, will give the better differentiation of individuals before and after recovery. There is furthermore, as evident in Table III, a slightly greater reliability of the difference between reaction before and after recovery in the case of galvanic-minus-blood-pressure measure than for galvanic response alone.

TABLE III

INDIVIDUAL REACTION TENDENCIES OF RESISTANT PATIENTS BEFORE AND AFTER SUCCESSFUL PHARMACOLOGIC TREATMENT

(Data represent the numerical values of class intervals or fractions of intervals as defined in Table I and illustrated in Fig. 6.)

	Blood Pressure Change	Galvanic Response	Galv.-B.P. Change
Before Treatment 12	1.53±0.19	1.05±0.35	−0.49±0.36
After Treatment 12	1.50±0.22	2.05±0.32	0.55±0.26
Difference	−.03±0.08	1.00±0.13	1.03±0.00
Crit. Ratio Dif./PE dif.	0.00	7.50	8.15
Chances in 100 of a true dif. greater than zero	50	100	100

No Improvement Following Treatment: The association of the observed physiologic changes with the "resistant" attitudes of the patients, and the relative unimportance of adaptation to the test situation as factor in our results is borne out by those instances in which the patient's attitudes were not altered by treatment. In two patients in whom resistant attitudes persisted after treatment as indicated by their overt behavior there was little evidence of change in the physiologic reaction picture, as evident from Fig. 7.

Illustrative Summary, unrecovered resistant patients:

Pt. A. C., female, age 30. Crucial questions were selected from material in the case history relating to a maladjustment due to her dissatisfaction with the feminine rôle and her inadequacy in an aggressive rôle. The first test followed her improvement from an acute stage during which she had been abusive, offensive and vituperative. Her answers were carefully worded, deliberate, controlled and evasive. She admitted only what she wished to admit, often answering one question by asking another. The patient made no attempt to use the interview to gain insight into her problems. Her behavior was practically unaltered following insulin treatment. Blood pressure before treatment was 100/70, after treatment 110/80.

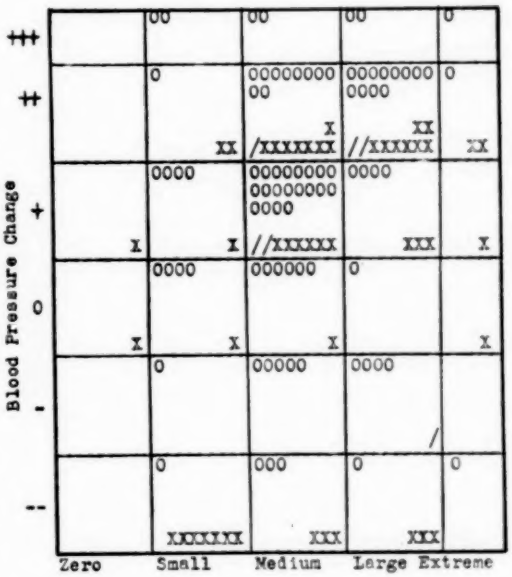
Overtly Passive Patients: In contrast with these reactions of resistant patients are the reactions of four whose psychotic attitudes were characterized by excessive overt passivity and submission (Fig. 8). Before treatment their reactions were located toward the middle upper right of the autonomogram and after treatment effecting apparent recovery in three and improvement in one of these cases they showed practically no change in the recorded physiologic reactions. It is to be emphasized that, although these patients were no longer depressed as they formerly had been, their attitude at the time of the final test was still one of overt passivity and submission, with persisting emotional reactivity corresponding to the relatively unchanged physiologic picture.

Illustrative Summaries, overtly passive patients:

Pt. E. E., male, age 39. The crucial questions were selected from material in the case history and related to the patient's ideas of self-reproach, self-condemnation and worthlessness apparently precipitated by an act of cunnilingus, his obsession that he was condemned to live forever, his passive attitude to his wife and men friends, his alcoholic excesses during which he showed overt aggressions toward wife and family, and to his gratification at being able to shoot par golf. During the first test he was eager to admit that he had sinned and that he was condemned. He did not argue, did not exhibit resentment, and made no attempt to defend himself against criticisms. Following treatment with matrazol he exhibited clinical recovery. He was co-

OVERT PASSIVITY; EFFECTS OF TREATMENT

Reactions to Crucial Ideational Stimuli
O = Before treatment, 4 cases
X = After treatment with recovery, 3 cases
/ = After treatment without recovery, 1 case



Log Conductance Change
(Palmar Galv. Response)

FIG. 8

operative, agreeable, gave appropriate rationalizations of his previous psychotic behavior. He was receptive to explanations and eagerly accepted reassurance. Blood pressure before and after treatment was 118/80.

Pt. R. E., male, age 33. Crucial questions were selected from material in the case history and related to submissive attitudes, to an inadequate sex adjustment with his wife, and to a general lack of forcefulness. He had a cringing passive attitude toward

the test situation. Answers to questions were characterized by plaintive querulous rationalizations, a readiness to agree, a weak defense against specific criticisms. On the second test following metrazol treatment the patient was improved in that he gave more appropriate replies. He was still acquiescent, agreeable and showed a willingness to be passive and to be humiliated. Blood pressure before treatment was 136/86 and after treatment 134/90.

Confirmatory Evidence: The results presented in this study offer an additional link in a chain of related evidence. Reduced galvanic reactivity in psychotic states has been frequently observed and the evidence has been summarized (*14*). In a study with Miss Heath (*22*) large galvanic and small blood-pressure responses to conditioning stimuli were found associated in normal individuals with a "comfortable adjustment to life situations." In a re-evaluation of their data on patients with compulsion neuroses Solomon & Fentress (*34*) found that when reactions measured in resistance change were corrected for resistance level there was a tendency toward small galvanic and large blood pressure reactivity. In psychotic patients Darrow & Solomon (*24*) found "irritability" characterized by large blood-pressure and small galvanic responses. Darling (*11*) in a study of autonomic activity of behavior problem children at the Institute for Juvenile Research found those children with the larger galvanic responses and the lower systolic blood-pressure levels more cooperative and less actively resistant than where the opposite condition prevailed. A recent compilation of our own data on reactions of patients without insulin and metrazol treatment (*23*) has shown that a group of eight patients selected because of their manifestation of hostile resistant behavior at the time of the test and a group of 10 patients selected because of their cooperative attitudes and partial or complete remission of psychotic symptoms showed the same general differences in autonomic response, though to a somewhat less degree, than have been found in patients before and after successful pharmacologic treatment.

Interpretation of the Autonomogram: Our data show that following crucial ideational stimuli a rise in blood pressure is associated with reduced palmar galvanic response in the three groups of resistant patients and with larger galvanic reactions in improved or recovered patients. The autonomogram is an attempt to provide an interpretation of this fact in terms of what is happening in the autonomic nervous system. It is well recognized that blood pressure changes are a function of the balance between sympathetic and parasympathetic activity; or perhaps we may say with more exactness, owing to the existence of some cholinergic fibers in the sympathetic system (*3, 33*) it is a function of the balance between adrenergic and cholinergic influences. The further influence of adrenergic vasodilator nerves which may reduce blood pressure response under certain conditions should be kept in mind as a factor limiting the application of this general principle (*3, 4, 5, 8, 33, 36*).

The palmar galvanic response on the contrary, is unquestionably innervated by the sympathetic system, and possibly also by the parasympathetic system (*18, 29*), and the peripheral sweat mechanism is pharmacologically cholinergic (*9, 10*). We may, therefore, draw certain inferences regarding reactions in which blood-pressure change and palmar galvanic response to stimulation are two-dimensionally represented.

A reaction in the *upper right* corner of the autonomogram with a large rise in blood pressure and a large galvanic effect represents predominantly strong activity of the sympathetic division of

the autonomic system. This we infer because only sympathetic influences following excitation would commonly occasion both a rise in blood pressure and an autonomic discharge to the sweat glands.

A reaction in the *lower right* corner, with a fall in blood pressure and a large galvanic reaction represents a strong cholinergic type of response. This is inferred on the basis of the known depressor effects of parasympathetic excitation or cholinergic activity in producing a drop in blood pressure by vasodilatation and inhibitory effects upon the heart. In view of the recognized cholinergic character of the sweat mechanisms, and the functionally parasympathetic character of many of the concomitants of palmar sweating (*18*), this type of response is at least suggestive of a general cholinergic influence of some kind. The possibility of an actual parasympathetic innervation, as claimed by Kuré and his co-workers (*29*), is to be kept in mind.

The interpretation of reactions in the *lower left* corner of the autonomogram, with a fall in blood pressure and no galvanic response, is not offered in view of conflicting explanations indicated by the available literature.

A reaction in the *upper left* corner of the autonomogram may be interpreted as due to either neural or humoral inhibition of parasympathetic or cholinergic activity. That it may represent neural inhibition of parasympathetic or cholinergic mechanisms, may be deduced from the fact that the reflex release of vasomotor or cardiac mechanisms from parasympathetic influences may cause a rise in blood pressure even as it may produce a dilatation of the pupil (*1*, *35*), and from the fact that a rise in blood pressure, in the absence of palmar sweating, is presumably not due to general sympathetic excitation. This latter is inferred from Cannon's principle that excitation of the sympathetic system tends to affect sympathetic mechanisms as a whole, and from the fact that palmar sweat mechanisms have an unquestioned sympathetic innervation. That a reaction in the upper left corner of the graph might also be due to humoral influences such as adrenine (*2*, *18*, *21*, *27*, *28*, *30*, *31*) sympathin I (*6*, *7*) or pituitrin (*32*) inhibiting the normal response of cholinergic mechanisms is supported by several lines of available physiologic evidence.

Comment: From such an analysis it would appear that before treatment the psychologically resistant patients tend to respond to ideational stimuli by reactions characterized primarily by neural or humoral inhibition of the previously existing cholinergic activity, whereas following treatment these patients tend to respond to the same stimuli by a more uninhibited autonomic action predominanatly sympathetic (*25*, *26*) in type. (Reactions to sensory stimuli, not here considered, did not show this differentiation.) Before treatment psychologically resistant attitudes were characterized by blocking, lack of cooperation and impairment of free flow of thought. The general picture is one of inhibition. Physiologically our analysis of the autonomogram has led us to deduce a form of neural or humoral inhibition of autonomic mechanisms. Following treatment the patients are characterized psychologically by a free, ready, uninhibited response. Physiologically the autonomogram indicated positive sympathetic and cholinergic effects suggestive of a relatively complete emotional reaction.

In a group of as yet unpublished untreated cases we have observed paranoid and manic patients who during angry outbursts gave reactions toward the upper right hand corner of the autonomogram. This behavior ap-

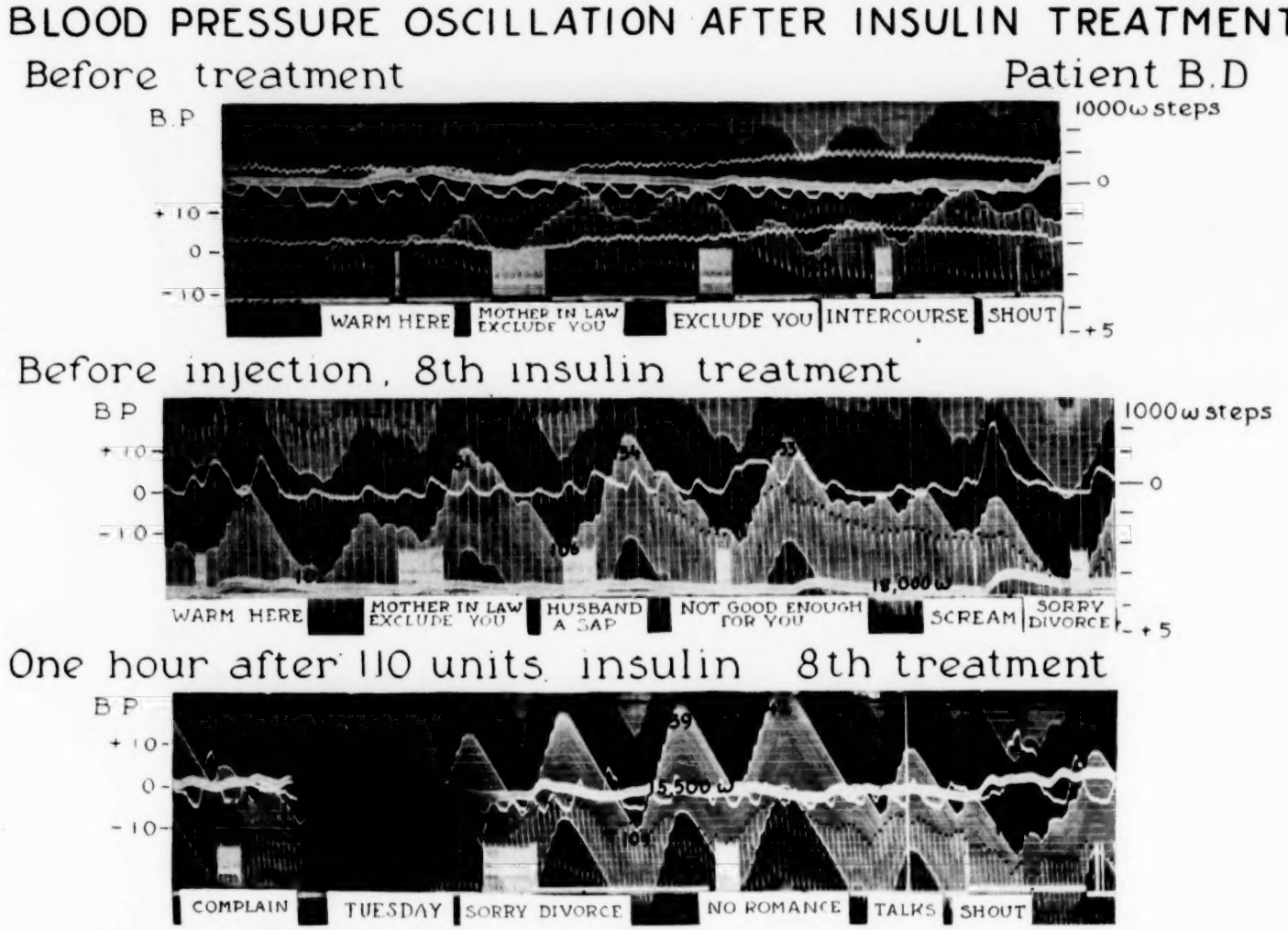

BLOOD PRESSURE OSCILLATION AFTER INSULIN TREATMENT
Before treatment
Patient B.D
B.P
1000ω steps
+10
0
-10
0
+5
WARM HERE
MOTHER IN LAW EXCLUDE YOU
EXCLUDE YOU
INTERCOURSE
SHOUT
Before injection, 8th insulin treatment
B.P
1000ω steps
+10
0
-10
34
33
108
18,000ω
WARM HERE
MOTHER IN LAW EXCLUDE YOU
HUSBAND A SAP
NOT GOOD ENOUGH FOR YOU
SCREAM
SORRY DIVORCE
One hour after 110 units insulin 8th treatment
B.P
+10
0
-10
39
15,500ω
108
COMPLAIN
TUESDAY
SORRY DIVORCE
NO ROMANCE
TALKS
SHOUT

FIG. 9

peared unrestrained, uninhibited and outgoing in contrast with the defensive, hostile, resentful attitudes generally characterizing the resistant patients. It should be added that even among the reactions of the resistant patients there were occasional instances of verbal and autonomic response which were of the more unrestrained outgoing type.

In the case also of the reactions of improved or recovered patients which occurred toward the upper right hand corner of the autonomogram it is our impression from a study of the replies that we are dealing with relatively complete uninhibited emotional responses to disturbing conflictual ideas. On the other hand reactions falling toward the middle right portion of the graph with moderate blood pressure and large galvanic responses suggest a strong "balanced" response of the two branches of the autonomic system suggesting less conflict and a more adequate satisfying rationalization. We conceive that in the case of such reactions the patient is able to think about and react toward his problems without being emotionally disturbed by them. This observation would indicate that well directed psychotherapy might prove beneficial in those improved cases with persisting high blood-pressure reactions.

Reactions During Insulin Shock: In the attempt to determine physiologic changes during treatment which might contribute to the differences in response observed before and after treatment we have recorded physiologic reactions during the course of insulin shock. In association with an increase in pulse pressure characterized by an extreme drop in diastolic pressure and a rise in systolic pressure, our records have shown a great increase in the fluctuations or oscillations in blood pressure (of around 20 mm. Hg amplitude and of 10 to 30 seconds per cycle) as shown in Fig. 9. The first section is the record before insulin, in which the fluctuations are not marked. The second shows the presence of an oscillatory effect on the 8th treatment before any insulin has been injected. The last section shows the maximum effect noted during insulin. It will be observed that the record of systolic blood pressure obtained by our absolute method and the relative record obtained by the sphygmomanometer both show these oscillations. We emphasize that auscultation more frequently than not will miss the higher and lower levels of these fluctuations. The oscillations are independent of the respiratory cycle. Similar extreme oscillations have been frequently observed in patients and normal persons subjected to low oxygen pressure, by Kraines and Darrow.[5] This is significant in view of the evidence offered by Gellhorn (*25*, *26*) of the simularity of physiologic effects of anoxemia and of hypoglycemia.

The large rhythmic oscillations in blood pressure recorded during hypoglycemia suggest an impairment of the normal sensitivity to slight changes in pressure in those (carotid sinus?) regulatory mechanisms which normally maintain blood pressure at a relatively even level. The oscillations here observed apparently subject the entire organism to rhythmic extremes of pressure which are at least suggestive of the rhythmic extremes of externally imposed pressure employed in the treatment of Berger's disease. That frequently repeated treatments of this kind might have far reaching, even therapeutic effects upon the vascular bed and homeostatic neuro-regulatory mechanisms throughout the body, including the brain, is worthy of consideration.

Summary: 1) Simultaneous records

[5] Unpublished study.

FIG. 9

of systolic blood pressure and palmar galvanic (sweating) responses during a standardized psychiatric interview situation revealed correlations between autonomic reactions and psychologic "resistance." When data on reactions of the two differently innervated autonomic effectors were plotted on two-dimensional graphs, "autonomograms," it was possible to deduce events in the autonomic system which were conceivably related to the patients' resistant attitudes.

2) One group of patients manifesting before pharmacologic treatment an attitude of psychologic resistance involving hostility toward the examiner or toward the testing situation was characterized by *large* blood-pressure reactions and *small* galvanic responses to crucial ideational stimuli.

3) Another group of patients manifesting an attitude of psychologic resistance involving perplexity in discussing or evading their emotional problems likewise showed *large* blood-pressure reactions and *small* galvanic responses to these stimuli.

4) Following pharmacologic treatment and clinical recovery in both these groups of patients the autonomic responses were altered to show *unchanged* blood pressure and *larger* palmar galvanic changes.

5) Patients whose resistant attitudes persisted and were unchanged by treatment revealed *no* change in the character of their autonomic responses.

6) Patients who were overtly passive and cooperative before and after treatment showed large blood pressure changes and large galvanic responses before treatment and these remained *unchanged* after treatment.

7) On the basis of known physiologic facts underlying interpretation of the autonomogram it is inferred that large blood-pressure and small galvanic responses in resistant patients indicate selective neural or humoral inhibitory effects upon certain autonomic mechanisms. It is inferred that improvement or recovery involves a decrease in these inhibitory effects and favors increased sympathetic reactions in combination with, and partially balanced by greater cholinergic responses to ideational stimuli.

8) Continuous recording of autonomic changes during insulin shock treatment revealed wide relatively rapid oscillations in blood pressure which may be significant in interpreting effects on the autonomic and vascular systems.

We are indebted to Drs. H. Douglas Singer and Paul L. Schroeder for rendering the facilities respectively of the Illinois Psychiatric Institute and the Institute for Juvenile Research available for this research. We are also indebted to the Illinois Department of Public Welfare, to members of the staff who gave assistance, and to Mrs. M. Wright under W.P.A. for stenographic assistance.

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NOTE ON PSYCHOANALYTIC TERMS USED IN THE FOLLOWING PORTION OF THIS SYMPOSIUM

EVERY SCIENCE DEVELOPS a technical terminology which describes the phenomena it studies with greater brevity and precision than can be achieved by popular expressions. In this communication an effort is made to avoid technical terms as much as possible. A few seem indispensable, and since they will probably appear in other articles dealing with psychoanalytic material, the following brief discussion of them is given:

"Masochistic" implies a tendency to maintain and even get satisfaction, conscious or unconscious, from a suffering situation. If conscious and intense, it may go to the extent of being a masochistic perversion. These patients unconsciously, repeatedly, established unhappy relationships which they neither escaped nor changed, but in which they continued to "stew". These attitudes and situations were repetitions of previous ones of childhood, to the parents. When the same attitudes and reactions, for example the expectations and resentments, which appeared in childhood to the parents, are repeated to teachers, bosses and others in adult life, these persons are referred to as "parent-substitutes". When they develop toward the analyst, are "transferred" to him, they are spoken of as "transference manifestations". The term "oral" is used to qualify the type of "dependence". It means very literally pertaining to the mouth and derives from the fact of the child's dependence upon the mother's breast. The nursing situation becomes the pattern of later situations of dependence upon other human beings, and being fed by someone becomes a symbol of love, protection, dependence. When an adult, consciously or unconsciously, craves assistance and dependence in the sense of the child upon its mother, it is regularly observed that this is represented in the dreams by being fed. Experimentally, oral attachments are easily demonstrated *in statu nascendi*, by giving a kitten milk, a puppy a bone, or a child candy. They want more, come again, become orally attached, and have to be "weaned". In adult life, when such attitudes, consciously or unconsciously restrained, are directed toward persons of the same sex, they may attain a passive homosexual coloring which if strong becomes very distasteful to the individual. Most men, even if they accept a passive dependent relationship to a woman, cannot tolerate being in such a relationship to a man. Their masculine pride demands that they be first, the leader, not the follower. Since everyone retains some of these early wishes to be fed, cared for, dependent, passive, this conflict is a general one. Persons who sense these trends in themselves usually feel weak, inferior, not masculine enough, and "overcompensate" by trying to be very defiant, rebellious and aggressive, in a way that is usually very hostile to others. This hostility, although it may be unconscious, may give rise to a sense of guilt, conscious or unconscious, which "inhibits" aggressiveness because it is too hostile, and so causes inner blocking or "self-thwarting". The passive dependent wishes may be "self-thwarted" by the masculine pride, which demands strength and constantly fights against such weaknesses.

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PSYCHOANALYTIC STUDY OF A CASE OF ESSENTIAL HYPERTENSION

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THE OBSERVATIONS DESCRIBED in this article were made in the course of a systematic clinical investigation conducted at the Chicago Institute for Psychoanalysis. The objective of this clinical study was to explore the psychological processes and the personality structure of patients suffering from essential hypertension. This investigation was undertaken in the hope that a systematic study of the emotional life of hypertensive patients by the psychoanalytic method, continued over a long period, would throw some light upon the still open question concerning the etiological rôle of emotional factors in the development of this widespread condition. At the same time the aim of this study was to establish the possibilities of psychotherapy in essential hypertension.

It is common clinical knowledge that acute emotional tensions have an influence upon the height of the blood pressure.[1] A common experience is that a patient who is in an apprehensive mood while having his blood pressure taken, shows higher readings than after he has been calmed down by the physician's reassurance. Animal experiments have corroborated the clinical findings and have shown that under the influence of rage and fear, the blood pressure rises (*3*). The influence of acute and intensive emotions on blood pressure can be observed in patients whose blood pressure is normal, as well as in those whose blood pressure is chronically elevated. It has also been observed in hypertensives whose condition is caused by renal disease. These observations in themselves do not allow any etiological conclusions concerning the rôle of emotions in the causation of chronically elevated blood pressure. They account only for the transient fluctuation of the blood pressure.

Another important clinical finding described by different authors is that most essential hypertensives show marked neurotic personality traits. Neither does this observation allow any definite etiological conclusions because the neurotically disturbed emotional life and high blood pressure may be parallel manifestations of a third factor (constitution); or the hypertension might contribute to the development of neurotic tendencies; or, the hypertensive state may be the result of a long standing neurosis. The opinions of different authors are divided on this subject.

We expected to obtain different kinds of information from the psychoanalytic study and therapy of such patients. In the first place, the psychological observations obtained by the method of psychoanalytic technique promised a

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I wish to express my thanks to Dr. Walter W. Hamburger for the thorough physical examination of the patient.

[1] Compare with the review of the literature of E. Weiss in this issue.

more intimate insight concerning the influence upon the blood pressure, not only of acute emotional states, but also of chronic emotional tensions as they can be observed in neurotics. Furthermore, the psychoanalytic study of cases gives a detailed picture of the personality development from early childhood on, which might throw light upon the development of the hypertensive state. Finally a comparative study of a series of patients suffering from essential hypertension may answer the question whether or not there is a definite personality structure which is characteristic for these patients. Apart from these theoretical objectives, we hoped to find a therapeutic approach based on etiological knowledge. In the following an attempt will be made to 1) give a dynamic picture of the personality make-up of a hypertensive patient; 2) to correlate the fluctuations of his blood pressure with his changing emotional states; and 3) to establish whether or not there are specific emotional tensions which have a specific influence upon the blood pressure.

I. The Patient's Personality and its Development

A. THE PRESENT PICTURE

The following observations were made during the analysis of a 47 year old male patient who was suffering from a pronounced though not excessive essential hypertension of the fluctuating variety. The patient's systolic blood pressure fluctuated between 175 mm. and 136 mm. and the diastolic between 120 mm. and 92 mm. This condition is of two years' duration.[2]

The patient was a married business man of Swedish descent with a distinctive educational and family background. He had four children, two older boys and two girls. He occupied an important and responsible but not the highest position in a large concern.

The patient's father died young of an acute infectious disease, his mother of a stroke when 73 years old. The patient drinks coffee occasionally and smokes from 20 to 40 cigarettes a day. The physical examination of the patient revealed a well developed, well nourished, somewhat obese, middle-aged man weighing 209 pounds. There was a distinct odor of alcohol on his breath. There was a moderate arcus senilis of both eyes. Liver dullness was two to three fingers below the costal margin, but no evidence of liver tenderness. The second aortic tone was moderately accentuated. There was a questionable enlargement of his spleen. His urine showed a trace of albumin and a considerable number of pus cells in the centrifuged specimen. Hemoglobin was 90; white blood count 7,600. There was a not undue, very moderate arteriovenous nicking in the retinal vessels with no increased tortuosity of the capillaries. Electrocardiographic examination showed a slow, regular heart beat with a slight tendency to left axis deviation and a moderate amount of slurring and notching in QRS in the 4th lead.

When I saw the patient first, he showed an extremely pronounced self-consciousness, with a vivid sense of inferiority. He constantly compared himself unfavorably with others, had little confidence in himself, tended to undervalue his efficiency, and was always doubtful about the merits of his accomplishments. At the same time, he was very ambitious to excel and turn out perfect work. He was definitely a retiring type, inconspicuous, a conformist, always polite avoiding contradiction. His ambitions to progress

[2] Compare with the following article of Leon Saul where the typical personality structure of seven analyzed hypertensives is summarized.

and to outdo the others remained restricted to his fantasy and did not appear on the surface. It soon became evident that this overt attitude of modesty and compliance put him under an extreme pressure and created intense inferiority feelings in him. These became most tormenting in relation to his chief. The patient never would contradict his chief, would follow his suggestions, accept blame while talking with him; but after he left the office, he was filled with self-contempt and would tell himself, "You should have answered. You should have said, No! You should have demonstrated to him that he was not right. You are no good and you never will be any good". This self-depreciatory attitude usually became so unbearable that he would have the urge to drink. Alcohol dissipated his sense of weakness and inefficiency. As soon as the alcohol began to make its effects felt, his spirit was lifted, he felt courageous and strong. But apart from the effect of the drug, the act of drinking itself had the significance of a rebellious act for him. He secretly enjoyed the feeling that in the middle of the day during office hours he escaped his duties and indulged in a forbidden activity. In this alcoholic mood, he would also indulge in promiscuous sexuality in a rebellious spirit against limitations imposed upon him by external social standards and by the voice of his otherwise so strict conscience. Obviously these alcoholic and sexual escapades relieved his sense of inferiority because under the influence of alcohol, he dared to commit such offenses as he would never have ventured without alcohol. But soon after he thus successfully escaped the pangs of inferiority feelings, he ran into a new conflict, that of guilt. For after he had committed all these forbidden sexual and non-social acts in order to show his independence, and thus escape his inferiority feelings, his conscience began to work and made itself felt in the form of remorse.

The patient's attitude in his professional life closely paralleled his attitude towards his wife. Here also, overtly he subjected himself to all requirements of the marital state but he secretly rebelled against its restrictions. His promiscuity to a great extent was rebellion against the marital chains. At the same time, he had a deep affection for his wife which no other woman has shared. His extramarital relationships were all of a superficial nature.

In brief, the most conspicuous feature in his make-up was this double attitude of overt subjection to external code and to his conscience, with an extremely strong emotional rebellion against this submission. This internal rebellion, however, did not show itself in any other way than in his drinking and occasional promiscuity, both of which had the emotional significance of a short circuit or a vent to relieve emotional tension—particularly his rebellious feelings against every external and internal restriction to which he submitted himself otherwise to an extreme degree.

B. THE UNCONSCIOUS DYNAMIC BACKGROUND OF THE OVERT PICTURE

During the course of his psychoanalysis the deeper dynamic background of this surface picture has been worked out. His rebellious, aggressive attitudes against the social restrictions of marriage, against his boss, against routine,—aggressive attitudes which he never could express openly and freely, were the reactions to a strong passive, masochistically colored feminine tendency and wish for dependence. With the progress of the analysis, more and more unconscious passive homosexual material came to the surface, both in dreams and in the transference. This

feminine tendency had definitely a masochistic tinge. In his dreams he was usually attacked. In other dreams, women appeared in the masculine rôle, even equipped with male anatomy. These masochistic and feminine attitudes also came into expression in day fantasies, in which he imagined his chief attacking, rebuking and abusing him. In this passive masochistic attitude, two elements were clearly discernible—1) a guilt component, and 2) a feminine element. The masochistic passivity was a combination of guilt and feminine submissiveness. By being abused and attacked, he relieved his guilt feelings and at the same time obtained feminine passive gratification. The guilt feelings came from his rebellious aggressiveness and extreme destructive competitiveness, which were reactions to the deep passive feminine attitude. The well known neurotic vicious circle was solidly established in him: His unconscious, masochistic feminine wishes hurt his masculine pride and drove him to rebellion, increased his competitiveness and ambition. These overaggressive tendencies, however, created guilt and fear which made the struggle of life too strenuous, exhausting and repulsive for him and thus intensified his longing for dependence and retreat. The thus increased passive dependent wishes, however, could not be accepted by his ego which was educated according to the accepted standards of his environment, namely, to consider success and efficiency and victory in the race of life as the highest virtues. Under the pressure of this deeply entrenched ideology of success, he had to struggle relentlessly against his deep longing for relaxation and dependence and continue the competitive game of social life. However, in distinction to many other cases who show the same vicious circle of emotional life, he was unable to give expression either to his aggressive ambitions or to his wish for passive dependence. Fear and guilt blocked the expression of aggressiveness and the internally accepted social standards prohibited him from giving in to his wish to escape the struggle of life. His aggressiveness and his protest against passive submission found a feeble expression in the adolescent behavior pattern—in surreptitious drinking and forbidden sexual acts. To some degree he gratified some of his submissive and dependent longings in giving his wife full control of their social life, expecting her to make all important decisions, and assuming towards her the rôle of an adolescent towards his mother, a peculiar mixture of obedience and surreptitious revolt. In his dreams, however, he regressed even further back than adolescence, way back to the early dependent attitude of the child toward the mother (oral dependence). A typical expression of this tendency was dreams in which he escaped the difficulties of life by seclusion and returning to mother nature in a somewhat Rousseau-ic manner. Some of the dreams were classical examples of womb fantasies: he saw beautiful and mystical, wild spots in nature; deep pits filled up with crystal clear water where big penguin-like birds rested peacefully and he together with them. The analysis of these regressive dependent tendencies led us back to a period of his life in which he must have reacted with great rivalry towards his eleven year younger brother, envying the mother's care for the baby and the passive gratifications of the little child.

The dynamic picture was one of an extreme polarization of the emotional life; on the one hand, a wish towards the infantile rôle of dependence and the feminine rôle of submissiveness and passivity, counterbalanced by the opposite attitude of ambition, perfection,

and masculine superiority. These two opposite tendencies mutually reinforced each other. The passive regressive tendencies hurt his pride and stimulated his aggressiveness, whereas the aggressive competitive tendencies created fear and a longing toward the security of the passive situation of being loved and cared for.

The here described polarization of these two opposing psychological attitudes reinforcing each other in a vicious circle, is a picture very commonly found in neurotic persons. It has been described by my collaborators and me in peptic ulcer cases (*1*), and in certain delinquent types (*2*). The same emotional conflict was most elaborately and convincingly described by Horney (*6*), who even went so far as to postulate this conflict between competitive ambition versus the wish to be loved and taken care of, to be a nuclear conflict, typical for the contemporary neurotic in our competitive Western civilization. The ubiquity of this conflict in our times does not mean, however, that all neurotics have the same personality structure. The psychoanalytic study of a great variety of neurotic patients taught us to recognize many different ways and means by which different personalities succeed in relieving the emotional tension resulting from this central conflict. Thus, for example, we have learned that peptic ulcer patients usually succeed in expressing their ambitious drives toward accomplishment and responsibility, frequently in aggressive business activities, or in administrative or organizational work. The opposite tendency, which is a reaction to this strenuous ambition: their longing for dependence and being loved and taken care of, is drained by organic symptoms, namely, by the increased functions of the stomach. The stomach is stimulated by the repressed unconscious tendencies to be fed, which since early childhood are emotionally linked with the wish to be loved. Also certain delinquent types freely express their aggressiveness and the wish to be tough and independent which they amply gratify in their adventurous life. Only the careful exploration of the depth of their emotional life can reveal the soft nucleus, the wish for dependence and security. This unconscious wish they satisfy when captured and imprisoned; then they freely indulge in the wish for shelter and retreat. Many prisoners' peculiar attachment to the prison, their unconscious wish to be recaptured and thus to escape from the struggle of life into the security of the prison, has been amply demonstrated by the psychoanalytic study of prisoners (*2*), and has also been recognized by the intuition of novelists (*4* and *5*).

What made this hypertensive case so different from the peptic ulcer personalities or the delinquent types and other neurotics in which this same vicious circle is a central issue, was the patient's extreme inhibition to satisfy either of his two opposing major trends: apart from the two inadequate vents, promiscuity and drinking, he was unable to express any aggressive independent wish, but at the same time he was equally unable to satisfy freely his longing for passive dependence. This strong inhibition to satisfy either of the two opposing major sides of his nature, his rebellious independence as well as his dependence, accounts for the impression which he made on the observer of being in a permanent emotional tension: a boiling volcano before eruption, but never erupting.

This inability to express these two opposing attitudes explains the peculiar neutrality which was so characteristic for his human relationships: always polite and modest yet not extremely submissive and humble, outwardly complying but always giving the im-

pression of a tacit resistance. The analysis revealed, that whenever he complied with the request of another person, especially of a superior, he immediately afterwards in fantasy rebelled against it without being able to give free expression to this internal revolt. It is no exaggeration to say that he was paralyzed in every emotional expression, each of the two polar opposing tendencies blocking the expression of the other.

This emotional paralysis accounts for certain recurrent characteristic dreams in which he undertook to do something (to catch a train, to go play golf, etc.) and was unable to do so. (His feet did not respond, or he could not put on his shoes, etc.) these dreams were accompanied by a feeling of utter futility. The deeper inquiry showed that even the only vents by which he could express his rebellion and independence, his drinking and sexual escapades, were condensation products of the two opposing tendencies. In his sexual relationship to women, there was a great amount of secret passive gratification (mainly through identification with the sexual partner); and his drinking, apart from its surface significance of an adolescent forbidden act, at the same time gave him the possibility to flee from all responsibilities of life and indulge in a carefree Nirvana-like sensation. It is no exaggeration to say that the alcohol bottle was the direct substitute for the mother's breast. Like feeding in his childhood, now drinking was able to relieve all unpleasant sensations, dissipate all worries, and give him a deep feeling of relaxation and happiness. Because it served both purposes to express rebellion and also to gratify his flight from responsibility to passive relaxation, drinking became a dangerous symptom. This explains why his conscious struggle to give up drinking had to remain ineffective.

C. HOW THE PRESENT PSYCHODYNAMIC STRUCTURE CAME ABOUT—BIRD'S EYE VIEW OF THE LIFE HISTORY

As will be seen, this emotional tension, resulting from two equally strong opposing tendencies blocking each other, was the psychodynamic situation which could be brought into correlation with this patient's high blood pressure. Therefore it might appear irrelevant for this study to enter the genetic problem as to how this emotional impasse came about during his life history. If it were true, that such a chronic emotional tension might produce a chronic elevation of blood pressure, the history of this condition is of secondary importance. In different cases, the same emotional blocking might come about in different ways; the important question is, whether or not, if present, it necessarily leads to high blood pressure. In order to decide this latter question, above all it must be established, whether or not this type of chronic emotional tension is characteristic for hypertensive patients. Saul in his article to follow summarizes our observations concerning the characteristic personality structure of hypertensives. His summary shows, however, not only that the actual emotional situation prevailing in adult hypertensives shows great similarities in different cases, but also that the developmental history shows certain parallel features. Therefore I shall try to draw a brief sketch of this patient's emotional development.

Only the most important facts of the life history will be mentioned, only those occurrences and emotional experiences which apparently have contributed to the development of the above described psychodynamic situation.

The patient came of an intellectual. refined family, and was born in Sweden,

The family came to the States when the patient was three years old. He was one of six children, an older brother died before the patient was born. The patient was the second of three brothers who were born in three successive years. Then came a five years younger sister, and finally his younger brother, eleven years younger.

As a young boy, the patient was in every respect the outstanding member of the family. His brothers looked up to him more or less as a hero. He could fight the battles of the younger boys. He was inclined to extreme outbreaks of rage, was absolutely fearless, played an astonishing game of football and baseball. In his first two years of public school, he resented the routine which was then required and rebelled against one of the teachers quite violently. His being sent home from school for unruly behavior became a regular occurrence. He still retained for a long time his superiority over his brothers and other boys. He was not only the best student in his grade, but probably the best student in the school. The whole family and everybody who was in contact with him, had the greatest expectations of him.

When he was twelve years old, his father died. He felt he should cry as all the other members of the family did, but he had no true desire for it.

Gradually, the patient lost his leading position in the family. Already in the first college years he began to slip, both in athletics and in scholastic achievements. As a result he developed a severe depression. He was still an excellent student and a good athlete but both of his brothers began to catch up and even surpass him. In his high school days and college days the patient made friendships with socially outstanding boys, much wealthier than he was. When he finished college he obtained a position in a concern owned by one of his friend's families. Leaning over backwards, he accepted in this company a menial position which was connected with extreme discomfort and even degradation. During this time he developed his second severe depression. Soon after he recovered from his depression, he married a socially outstanding girl and through this marriage he entered into a group much wealthier than his family was. Although he obtained a very excellent business position, the patient had to struggle desperately to live up to the standards of his circle. About in the 12th year of his marriage, he started to drink, which was the only means of getting rid of his apprehensive depressive moods, which with great regularity every morning after awakening, began to torture him. Looking back on his life, back to adolescence, the patient was never free from a strong self-critical depressive state of mind, which gradually grew worse and worse.

Viewing this history from a distant perspective, we see the gradual metamorphosis of an over-aggressive, successful, domineering young man, determined for leadership, into a shy, inhibited, conforming, overly modest and unexpressive person. The aggressive and courageous spirit of his early years appears in the adult only in the form of two neurotic behavior patterns —in promiscuity and drinking—in this typically adolescent way of showing masculinity and a tough independent spirit.

The explanation of this metamorphosis will be found in the analytical material, by means of which we have in part recovered and in part reconstructed those emotional experiences which deflected the course of the patient's masculine development and broke the spirit of this promising young man.

The History of the Emotional De-

velopment: For a long period during his treatment, the patient's memory material consisted mostly of recollections of defeats and failures, intimidations and inhibitions. The early period of aggressive leadership did not appear in his associations, was obviously overshadowed by gloomy memories dealing mostly with his internal insecurity, with a continuous struggle against his inhibitions. Although the intimidating experiences which gradually led to the development of an extremely inhibited personality go back to his early childhood, it was not before puberty that they visibly influenced the overt picture and changed his relationship to his brothers from leadership into a slow but continuous falling back.

For a long period the patient did not recall at all the extreme rage outbreaks characteristic of his earliest childhood. This free expression of anger in childhood is in such a contrast to his later inability to express any hostile feeling, that it can only be explained by a later extreme repression of all hostile impulses. This might account for the fact that he forgot this early aggressive attitude to an astonishing degree and that memories about his early aggressive behavior and temper tantrums were recovered only in the progressed phase of his analysis.

One of his earliest memories is that when three or four years old he climbed up on his father's back, fell and suffered a concussion. About in the same age, he remembered the first spanking by his father who punished him for his violent temper. After this punishment the patient felt extremely humiliated. It was mentioned before that in the first school years he openly rebelled against school routine and was continually punished.

Right at the beginning of his treatment he recalled a series of external events of intimidating nature.

When he was four years old he fell into water and was almost drowned. From this incident, he retained up to the present date some fear of diving.

When he was five years old, in kindergarten, he locked himself into a closet with another boy, could not get out and became extremely panicky.

When he was five he locked himself out on a playing porch on the third floor, and when he tried to climb down, he fell down one story.

One of his most outstanding memories is of an older man who took him and his brothers out fishing, but then because of his unruly behavior, wrapped him up with a fishline. He never could forget the impotent rage which he felt being bound up this way. Struggle against external pressure was one of the leading motives in his associations.

The most serious intimidations were, however, connected with his sexual feelings. His sexual curiosity appeared early in the pre-puberty period and occupied most of his interest. As long as he can remember, he always felt extremely shy and timid toward girls. Everything connected with sex, he considered low and dirty but at the same time he had an extreme longing for it. As an adolescent, he did not dare to touch even the hands of a girl. His first sexual intercourse was with a prostitute, when he was 17 years old. Afterward, he felt morally soiled. He confessed immediately to his mother and did not dare to give in to his sexual impulses again until he was 21 years old. After this time he had casual sexual relationships, but after them always felt terrifically degraded.

In a later period of his analysis he was able to remember probably his first sexual trauma. When three or four years old, his father caught him masturbating and reprimanded him. About the same time he had a recurrent nightmare of an ogre which appeared at the end of a dark corridor and threatened him.

His father, who died when the patient was 12 years old, played apparently the most important rôle as an object of fear and hostility. He thought that he ought to break the boy's aggressive spirit and rebelliousness against every external pressure and routine and made a point of teaching him how to lose. Patient was about eight years old when his father began to take him out to the golf course, beat him at golf repeatedly and tried to make him like to be beaten. Patient remembered his senseless rage when he was beaten in any competitive game. It is interesting that even at his present age, the patient has the greatest dislike to go out to play golf with his chief. Whenever the chief asked him to go out to play golf, he wanted to refuse, did not dare to, accepted the invitation, but for days after, the analytic hours would be filled with broodings of the following kind: "Why did I accept? Why couldn't I say to the boss—'No, I won't go' ". In spite of this overt rebellion, his dream material gave ample evidence of the fact that this submission appealed deep down to his passive feminine longings and was a source of unconscious gratification for him.

The most important factor however which contributed to breaking his spirit was unquestionably the extreme inhibition of his premature and intense sexual desires by the very strict moral code of his environment and particularly his family. The so common puritanical rejection of everything related to sex was unusually pronounced in his childhood attitude.

Gradually the external intimidation by his father, school discipline, and the moral pressure of his environment, became internalized in the form of a severe conscience, the source of his intensive and continuous guilt feelings. Every manifestation of sexual interest, of aggressiveness and competition became connected with a sense of guilt. He could not win without feeling guilty for it: as a result of this guilt feeling a powerful internal self-thwarting attitude has developed in him. These unconscious guilt feelings explain why, when he later became a business executive, he never could discipline or dismiss anyone without the most severe remorse and self-accusation. He had several dreams in which he first was in the superior position and then compulsively had to identify himself with the underdog.

This self-thwarting attitude was the basis of his extreme self-consciousness, insecurity, inhibition about speaking publicly and persistent fear of losing his leadership. Only this self-inhibiting influence of his overly severe conscience can account for his gradual slipping back in scholastic achievements and athletics, in relation to his brothers. From early puberty on his life consisted of a desperate struggle against this internal self-thwarting tendency trying in vain to retain his former superior position. When his younger brother once made a remark that on one day of the year they are the same age, he threw him on the floor, shouting at him: "You may be the same age, but you never will have my physical power".

In school and college this struggle centered around scholastic and athletic achievements, and later during his married life, around income and social prestige. In his adult years his social circle took over the rôle of the competitor which his two brothers played in his youth.

It is not my purpose to give the full case history, only as much as is necessary to substantiate the following dynamic reconstruction of his emotional development.

This aggressive, and intellectually and physically outstanding young boy reacted to the external pressures he met in his early life, such as school routine and other customary restric-

tions of the latency period, with rebellion. This provoked his father who rationalised his emotional reaction to his son's aggressiveness with some educational theory and tried to break this little rebellious Oedipus. It seems that he succeeded only too well. As has been mentioned before, this submission to his father to which the little boy first gave in under external compulsion, gradually became erotized, or in other words, a source of a feminine gratification. As it can be so often observed, the ego made the best out of a painful situation. At first he was forced to submit and did it under protest; later gradually he began to like it. It must be emphasized, however, that this feminine masochistic attitude remained always unconscious in him. His conscious ego dominated by masculine pride never would admit it openly. This unconscious, masochistically colored, feminine, dependent attitude in combination with the more diffuse and intangible but equally powerful moral pressure, mainly represented by his mother, prepared the ground for the extreme sexual inhibitions and guilt feeling which the boy began to show after his eighth year. These sexual inhibitions hit his masculine self-confidence in its core.

As a continuation of the external intimidations his guilt feeling toward his brothers, forced him towards the *inferior position* which already previously had become erotized in relation to his father. Yet the previous position of superiority and leadership developed in him a sense of obligation to live up to the high expectations which everyone had toward him. Tired by these permanent efforts to maintain his leading position, he developed a keen longing for the comfortable dependent though inferior rôle of the small child. The birth of his younger brother, when he was 11 years old, unquestionably contributed to this regressive longing for the carefree position of the small child. While he had to make desperate efforts to hold on to his leadership and continue to play the rôle of the hero, there was the example of his little brother pampered by the mother and enjoying a comfortable carefree existence. His alcoholism—as became fully evident during the analysis—served the purpose of solving this conflict by satisfying both of the conflicting tendencies. On the one hand drinking meant for him a rebellious act, gave him a spurious feeling of superiority, eliminated his inhibitions, enabled him to give in to his promiscuous sexual tendencies, but on the other hand the alcohol bottle represented the milk bottle and the feeding mother. Intoxication gave him the same relaxed Nirvana feeling which he probably experienced in his earliest infancy during the act of suckling.

II. Relation between Emotional Tensions and Fluctuations of Blood Pressure

Among all the dynamic forces which participated in this complex dynamic equilibrium, the rebellious aggressive tendencies and the concomitant anxiety stood in direct relationship to the fluctuations of the patient's blood pressure. Although he never could express freely these hostile aggressive impulses, they were not deeply repressed into the unconscious. They appeared in aggressive fantasies or during his depressions in self-destructive attitudes. Whenever they were mobilized, his blood pressure rose, whereas in those periods in which he was relatively calm the blood pressure fell.

I shall submit now the observations concerning the relationship of emotional status and blood pressure readings.

At the beginning and the end of every analytic session the blood pressure of this patient was measured by a

TABLE I

I EMOTIONAL STATE: VERY DISTURBED		II EMOTIONAL STATE: SOMEWHAT DISTURBED			III EMOTIONAL STATE: CALM		
1937		1937		1938	1937		
Mar. 1	160/120	Mar. 4	150/104	Jan. 5	150/108	Mar. 19	138/ 92
Mar. 2	158/112	Mar. 5	168/118	Jan. 10	152/104	Mar. 22	136/ 94
Mar. 8	162/104	Mar. 16	140/ 96	Jan. 11	152/104	Mar. 26	138/ 96
Mar. 24	160/104	Mar. 17	160/106	Jan. 12	136/ 98	Apr. 1	142/ 96
Mar. 31	158/112	Mar. 18	146/ 98	Jan. 28	158/106	Apr. 2	140/100
May 7	160/110	Mar. 23	152/102	Feb. 1	156/102	Apr. 3	140/ 94
May 17	164/128	Apr. 23	140/106	Feb. 8	148/100	Apr. 6	136/ 92
May 25	174/124	Apr. 25	138/102	Feb. 9	150/104	Apr. 22	150/110
May 27	160/110	Apr. 28	152/102	Feb. 10	140/102	Apr. 27	164/120
June 1	154/114	May 4	136/106	Feb. 11	144/ 92	May 8	132/ 98
June 2	164/104	May 5	144/104	Feb. 14	148/100	May 24	142/106
June 10	172/122	May 6	154/110	Feb. 15	148/102	June 7	148/108
June 15	154/104	May 18	160/110	Feb. 16	146/100	Sept. 10	128/ 90
June 17	160/106	May 21	150/110	Feb. 21	150/108	Sept. 14	152/106
July 2	142/102	May 26	147/103	Feb. 23	142/ 94	Oct. 4	140/100
Sept. 28	168/112	June 3	136/ 96	Feb. 25	140/ 94	Oct. 12	142/106
Sept. 29	174/120	June 4	150/110	Feb. 28	140/ 98	Oct. 18	146/ 98
Sept. 30	164/110	June 8	148/106	Mar. 1	158/106	Oct. 19	142/100
Oct. 1	158/112	June 9	148/108	Mar. 4	148/ 98	Nov. 2	142/102
Oct. 11	156/110	June 11	154/104	Mar. 7	150/100	Nov. 5	146/ 98
Nov. 3	158/110	June 14	146/116	Mar. 16	144/ 98	Nov. 8	138/ 94
Nov. 17	160/110	June 16	144/106	Mar. 21	138/100	Nov. 11	140/ 98
Nov. 18	160/108	June 18	156/110	Mar. 22	146/ 98	Nov. 12	140/ 98
Dec. 13	166/112	June 29	158/106	Mar. 28	142/102	Nov. 15	140/ 98
Dec. 14	160/112	June 30	146/104	Apr. 6	148/110	Nov. 16	144/102
Dec. 23	170/118	July 1	156/106	Apr. 13	144/104	Nov. 29	148/106
1938		July 4	152/106	Apr. 15	142/100	Dec. 3	148/100
Jan. 6	168/114	Sept. 9	146/104	Apr. 18	150/112	Dec. 15	148/110
Jan. 14	156/106	Sept. 13	146/106	Apr. 22	156/108	1938	
Jan. 24	166/112	Sept. 16	150/104	Apr. 23	150/106	Jan. 4	140/108
Feb. 4	150/106	Sept. 20	152/110	Apr. 24	154/106	Jan. 17	140/ 90
Feb. 7	150/106	Sept. 21	162/112	May 5	152/108	Jan. 18	146/ 96
Apr. 20	158/104	Sept. 27	152/106	May 9	144/108	Jan. 19	140/ 96
Apr. 25	152/102	Oct. 25	170/120	May 11	152/106	Jan. 20	136/ 98
Apr. 27	158/106	Oct. 26	156/114	May 19	154/104	Jan. 21	136/ 92
May 1	166/116	Oct. 27	154/110	May 20	154/106	Feb. 2	144/ 92
May 2	156/112	Oct. 28	152/108	May 24	152/120	Feb. 17	134/ 92
May 21	162/110	Oct. 29	146/108	Oct. 3	158/110	Feb. 18	142/100
Oct. 11	166/110	Nov. 4	150/108	Nov. 3	146/104	Feb. 24	142/ 96
Oct. 12	146/104	Nov. 9	146/100	Nov. 7	156/102	Mar. 8	146/100
Oct. 13	170/110	Nov. 10	144/102	Nov. 8	166/108	Mar. 10	146/ 98
Oct. 14	148/106	Nov. 19	162/112	Nov. 9	144/ 96	Mar. 11	142/ 96
		Nov. 22	148/102	Nov. 14	148/ 96	Mar. 17	144/ 98
Average:	160/111	Nov. 24	148/104	Nov. 16	146/104	Mar. 18	136/ 92
		Nov. 26	148/104	Nov. 17	150/100	Mar. 29	136/ 98
		Nov. 30	152/106	Nov. 18	150/112	Apr. 14	136/100
		Dec. 1	150/108			Apr. 19	138/104
		Dec. 2	140/108	Average:	150/105	May 4	138/106
		Dec. 6	152/104			May 10	142/104
		Dec. 16	152/110			May 12	142/100
		Dec. 20	164/112			May 16	146/102
		Dec. 21	164/102			May 26	132/ 96
		Dec. 24	152/108			May 31	132/100
						June 1	148/102
						Sept. 8	132/100
						Sept. 9	138/106
						Oct. 4	140/ 98
						Oct. 5	140/ 98
						Oct. 6	144/ 96
						Oct. 7	132/ 92
						Nov. 4	140/102
						Nov. 15	150/106
						Average:	141/ 99

mercury sphygmomanometer and compared with the emotional state of the patient and the details of the analytic material. The blood pressure was taken at first by a physician who did not treat the patient and then by the analyst in order to establish the influence of special emotional reactions towards the analyst. However, in the vast majority of readings there was no noticable difference between the two readings. Furthermore, both observers took several readings.

These observations in Table I can be summarized as follows: In 201 sessions the patient's blood pressure was taken and compared with his emotional state. In 41 interviews the patient's emotional state was *very distrubed*, in 99 interviews *somewhat disturbed*, and in 61 interviews the patient was subjectively *calm*.

His average blood pressure on the basis of all readings was 149/105. During the very disturbed interviews, the average blood pressure was 160/111 and in the calm interviews 141/99. There were only two very disturbed sessions in which he had a relatively low blood pressure, and both occurred on a day after he had consumed a considerable amount of alcohol. Otherwise the blood pressure functioned almost as a barometer of his emotional state, being high when the patient is emotionally disturbed and lower when he is calm.

Because the patient came to a great number of the analytic sessions after consuming alcohol the question arose as to the direct effect of alcohol upon the blood pressure. In order to eliminate this complication, in the following chart only those blood pressure readings are considered which were taken when the patient was entirely sober.

As is seen in Table II, here there is no exception from the rule, namely that during the very disturbed sessions his blood pressure is relatively high (average 161/110 mm.) during the calm sessions considerably lower (average 142/98 mm.).

These observations show a clear correlation between emotional disturbances and change of blood pressure. It is important that in those days when the patient felt calm, did not show emotional conflicts, his blood pressure was only a little above normal. Therefore one is justified in saying that whenever a marked elevation of his blood pressure above normal was observed, it regularly coincided with a disturbed emotional state.

During the majority of the interviews the blood pressure remained about the same at the end of the session as it was at the beginning. In a number of sessions the blood pressure dropped or raised considerably—15 to 20 points. It is noteworthy that the examination of the analytical material during the sessions when the blood pressure dropped, showed marked relief from emotional tension, whereas in the hours when it rose, it showed increased resistance and discomfort.

The nature of the emotional state which was connected with elevation of the blood pressure can be briefly characterized as a depressed, tense, apprehensive mood, sometimes mixed with some aggressive irritation which, however, the patient never expressed openly but only referred to it in a descriptive calm fashion. When depressed, the patient turned against himself, depreciated himself and his work in many different ways. Such depressive states usually were connected with fearful apprehension. He was concerned lest on account of his inefficiency—which to be sure was merely imagined—he would lose his job and would not be able to support his family. Then his only escape would be suicide. In other sessions his self-destructive attitude was mixed with anger and embitterment directed against his superior but he

TABLE II

IN SOBER STATE

I EMOTIONAL STATE: VERY DISTURBED		II EMOTIONAL STATE: SOMEWHAT DISTURBED				III EMOTIONAL STATE: CALM	
1937		1937		1938		1937	
Mar. 1	160/120	Mar. 4	150/104	Jan. 10	152/104	Mar. 19	138/ 92
Mar. 2	158/112	Mar. 5	168/118	Jan. 28	158/106	Apr. 1	142/ 96
Mar. 31	158/112	Mar. 16	140/ 96	Feb. 1	156/102	Apr. 2	140/100
May 25	174/124	Mar. 17	160/106	Feb. 8	148/100	Apr. 3	140/ 94
May 27	160/110	Mar. 18	146/ 98	Feb. 9	150/104	Apr. 6	136/ 92
June 2	164/104	Apr. 25	138/102	Feb. 10	140/102	May 24	142/106
June 15	154/104	May 6	154/110	Feb. 11	144/ 92	Nov. 2	142/102
June 17	160/106	May 18	160/110	Feb. 14	148/100	Nov. 5	146/ 98
Sept. 28	168/112	May 21	150/110	Feb. 15	148/102	Nov. 8	138/ 94
Sept. 29	174/120	May 26	147/103	Feb. 16	146/100	Nov. 11	140/ 98
Sept. 30	164/110	June 3	136/ 96	Feb. 23	142/ 94	Nov. 12	140/ 98
Nov. 3	158/110	June 4	150/110	Feb. 25	140/ 94	Nov. 15	140/ 96
Nov. 17	160/110	June 8	148/106	Mar. 1	158/106	Nov. 16	144/102
Dec. 14	160/112	June 11	154/104	Mar. 4	148/ 98	Nov. 29	148/106
1938		June 14	146/116	Mar. 7	150/100	Dec. 3	148/100
Feb. 7	150/106	June 16	144/106	Mar. 22	146/ 98	Dec. 15	148/110
Apr. 20	158/104	June 18	156/110	Apr. 13	144/104	1938	
Apr. 25	152/102	July 4	152/106	Apr. 22	156/108	Jan. 17	140/ 90
Apr. 27	158/106	Sept. 20	152/110	Apr. 23	150/106	Jan. 18	146/ 96
		Nov. 4	150/108	Apr. 24	154/106	Jan. 19	140/ 96
Average:	161/110	Nov. 9	146/100	Nov. 7	156/102	Jan. 21	136/ 92
		Nov. 10	144/102	Nov. 8	166/108	Feb. 2	144/ 92
		Nov. 19	162/112	Nov. 9	144/ 96	Feb. 17	134/ 92
		Nov. 22	148/102	Nov. 14	148/ 96	Feb. 18	142/100
		Nov. 26	148/104	Nov. 16	146/104	Feb. 24	142/ 96
		Nov. 30	152/106	Nov. 17	150/100	Mar. 8	146/100
		Dec. 1	150/108	Nov. 18	150/112	Mar. 10	146/ 98
		Dec. 2	140/108			Mar. 11	142/ 96
		Dec. 6	152/104	Average:	150/104	Mar. 17	144/ 98
		Dec. 16	152/110			Mar. 18	136/ 92
		Dec. 20	162/112			Apr. 14	136/100
		Dec. 21	164/102			May 12	142/100
						Oct. 6	144/ 96
						Nov. 15	150/106
						Average:	142/ 98

never expressed these feelings in an emotional, dramatic fashion. Ideas of physically attacking his chief were not uncommon. In the course of his associations these aggressive thoughts regularly led to anxiety and then to self-accusations and self-depreciation. The consecutive phases of this emotional process could be clearly observed, how his hostile impulses created guilt and fear, then became inhibited and then like a boomerang turned back against his own self.

There is no doubt that the dynamic nucleus of his emotional difficulties consisted of hostile impulses. These led to fear and guilt and as the next step to his depressions. His emotional condition could be best characterized as a state of inhibited hostile aggressive impulses.

In the last part of his analysis, the patient lost entirely his depressions, and his emotional tension appeared only in the form of a tense feeling and some vague irritability. Most significant is the fact that during a period of two months during which the patient's emotional difficulties were reduced to a minimum, when he had no apprehensions about his job, felt calm and contented, his blood pressure did not show the usual extensive fluctuations: his systolic pressure, with the exception of one day, did not surpass 150 mm.; in the last three weeks of this period his diastolic pressure with the exception of one day never exceeded 100 mm. This is therefore significant, because viewing the whole period of the analysis, the variations of his systolic pressure were between 175 mm. and 136 mm. and of

the diastolic pressure between 120 mm. and 92 mm.

This analysis is still in progress. One cannot, therefore, as yet draw definite therapeutic conclusions from it, especially not concerning the hypertensive state. So much can be stated, however, that in the course of the analysis the patient has almost entirely recovered from his depressions and has his alcoholic tendencies under much better control. The analysis still cannot be considered as completed because although the depressions and apprehensions have disappeared, and the irritation towards his chief has completely subsided, the patient is still under considerable emotional tension, the ideational content of which is much less defined, however, than it was before. This tension consists mostly in a rebellious feeling against every external routine, and limitation. This emotional tension is definitely less than it was before, it has more openly an aggressive connotation and is not turned against himself in the form of depressions and self-accusations. So far as the blood pressure is concerned, in the last eight months the trend was toward a slow but definite decrease of both systolic and diastolic pressures. The day by day fluctuations have been around a somewhat lower level and their range is definitely smaller, with the exception of a period of a few weeks when an extremely traumatic external event upset the patient's emotional equilibrium to a considerable degree. A definite therapeutic conclusion will be possible only if the analysis succeeds in further diminishing the patient's chronic emotional tensions.

Summary

The day by day blood pressure fluctuations of a 47 year old male suffering from a chronic depression, chronic alcoholism and essential hypertension, have been compared with the daily psychoanalytic material. The patient's overt personality has been described and the underlying psychodynamic personality structure reconstructed and explained in the light of the emotional development which led up to the adult personality.

A definite correlation has been found between emotional tensions and fluctuations of the blood pressure. The nature of the emotional tensions has been identified as inhibited, but not deeply repressed aggressive impulses directed partly inward against the patient's own person in the form of depressions, partly turned outwards in the form of hostile feelings. These emotional states were mixed with an apprehensive worrisome state of mind. Finally it was observed that during a period in which the patient was in an exceptionally calm state, his blood pressure was definitely lower and showed considerably smaller fluctuations. During the last period of treatment, with the diminution of the emotional tensions, there was a slow but definite decrease of the day by day fluctuations, and a slow downward tendency of the average blood pressure level.

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HOSTILITY IN CASES OF ESSENTIAL HYPERTENSION

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I. INTRODUCTION

IT HAS BEEN KNOWN for a long time that acute emotional states can cause transient elevations of blood pressure (*2*), and it has been suspected that emotions may be of etiological importance in the chronic condition of essential hypertension (*4*). Just how critical a rôle the emotions play etiologically in this condition is not known, although some cases have been reported in which chronically elevated blood pressure has returned to normal after the patient experienced emotional relief (*9*). Nor is it known whether or not any specific emotional situation is correlated with essential hypertension, *i.e.*, whether any specific psychology of essential hypertension exists. Anger is the emotion connected with high blood pressure by the laity, an impression which is confirmed by scientific investigation (*1*) (*5*) (*10*) (*11*) (*12*). This communication describes the main psychological features of seven psychoanalyzed cases of essential hypertension. This series is of course very small, but the uniformity of the psychology is at least suggestive, and receives support from other cases, studied more briefly, and from the short reports of cases in the literature. The more thoroughly studied cases were two men and two women with essential hypertensions which ranged from 140 to 200 systolic over 80 to 130 diastolic. The blood pressures were recorded by mercury manometer before and after every analytic session. Correlations between the fluctuations of blood pressure and the psychological material are dealt with by Alexander in this symposium. Graphs of these daily blood pressures for periods of from several months to several years will be published elsewhere. Besides these four cases, psychoanalytic material was also available on three more psychoanalyzed cases whose pressures ranged lower. The patients were all examined medically.

References to the literature appear in Weiss' review in this journal and will not be repeated here. This paper is a report of an effort to determine whether or not any specific psychological features could be found in a small series of essential hypertensives. The conclusion is that such a correlation probably exists, but further study is required on these and on more cases, before a clear-cut answer can be given. The common findings in these few cases were 1) the status of a particular conflict situation, and 2) the status of the hostilities.

II. THE CONFLICT SITUATION

The central conflict situation was strikingly similar in the four cases. This conflict situation is a widespread one and its distinguishing features in these cases lay in its status and the way in

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which it was handled. In brief this conflict situation consisted of 1) a masochistic submissive and an oral dependent attitude, originally toward a dominating parent, leading to a masochistic submissive attitude to a dominating conscience, to the parent of the same sex, and to parent-substitutes in later life; 2) chronic, unsuccessful, unsatisfied rebellion and hostility in protest against this submission. The rebellion and hostility were conscious or near to consciousness and not expressed directly because of fear of loss of love. The submissiveness was not conscious and bitter hostility opposed making it conscious in the analyses. There was also rage at not getting the desired passive oral dependent gratification. Another prominent feature was excessive fear of heterosexuality, which was to some extent indulged despite the anxiety. The most characteristic general feature of all of the cases was that both the oral dependent wishes and the hostile aggressive impulses were internally inhibited and were never satisfied in life or in symptoms. These patients were neither passive and dependent nor hostile and aggressive. They could give in to neither trend. During periods when they could and did, their blood pressures were markedly lower.

III. Clinical Data

Mr. A. came with a complaint of anxiety. He was in his forties, with a hypertension fluctuating from 160 to 200 systolic over 110 to 130 diastolic, which had been increasing for the preceding ten years. He was the only patient of the series with marked arteriosclerosis and somewhat impaired renal function, 65 per cent phenolsulphothalien excretion. He was one of a number of children, and had been spoiled and dominated by his mother who also dominated the physically strong father. His mother made him work from the age of six to contribute to the family who lost their money at that time. He reacted with lifelong bitterness to being thus prematurely forced to work after the earlier extreme spoiling. She forbade sports as dangerous, and later forbade the patient to see girls other than those of his own faith. He obeyed despite his envy of the boys who engaged in athletics and in sexual play with girls. She set him the ideal of wealth, inspired him with excessive ambitions and great expectations, and forced him into marriage against his will with a girl of her own choosing. Thus his whole life, his work, his religion, his marriage, came to mean submission to the mother—"bending the knee" as he put it—and also being forced out of the earlier situation of maternal spoiling and protection into excessive ambitious activity. He tried in vain for many years to escape or rebel against this unconscious attachment to the mother. Finally he actually got a divorce and tried to indulge in sexual promiscuity and alcoholism. He even took a girl to the Orient in an effort to escape his fears and be free sexually. But the anxiety was too great and he was forced to give up the rebellion. The patient's hypertension always increased during these periods in which anxiety frustrated his attempts at heterosexuality. Apparently in an effort to escape the conflict with his dominating mother, this patient turned to his father. But although on the surface his relations with men were less acutely disturbing, the dependence and submissiveness toward them was even more intolerable than toward women. Again the patient rebelled, using unconscious hostility as his defence. This was most clear toward his boss to whom again he would not "bend the knee". Besides his hostility from rebellion against his dependence and submissive-

ness, he would rage at not getting the passive receptive satisfaction he demanded, *i.e.*, at not being able to be dependent on others, but being forced to ambitious independent exertion and responsibility. But his rage from rebellion and from frustration was never directly expressed. He was quiet and gentlemanly with all. His rage at his mother was conscious and at his boss nearly so, though he knew nothing of the source (the submissive dependent wishes). The unconscious structure is that of paranoia. In a typical dream he is in bed with a woman when a big man enters with a flashlight, and the patient tries to flee in anxiety. It is a nightmare. The big man is the analyst, the flashlight the analysis. The patient tries to flee from his tendency to give up heterosexuality and to become dependent upon the analyst. The positive Oedipus conflict was also overt and intense in this case. The unconscious masculine competitiveness was intense and there were dreams of direct sexual advances to the mother. The mother had evidently been seductive as well as dominating. Her domination and seductiveness intensified the patient's feelings of inferiority and hostility to the father, and drove him to further dependence upon the mother and to an anxious, submissive, masochistic attitude to the father.

A full description of the second male hypertensive appears in Alexander's paper. It is typical of the male hypertensives we have studied. The female cases are not so clear. Briefly, Mr. B. was in early middle age. His hypertension was of 2 years' standing and ranged from 135 to 175 systolic over 90 to 120 diastolic. He presented a picture almost identical with Mr. A.'s. Mr. B. also had a domineering mother who drove him into a dependent (oral) attitude to her and into fear of her, and into an anxious, submissive attitude toward the father, who in this case also dominated the patient. This patient, like Mr. A., conformed perfectly, was a model citizen, and a compliant, obedient, subordinate. But although he never showed it, his wish to defy the father, repeated clearly in his relationship to his boss, was close to consciousness. Like Mr. A. he dared not express it in the slightest degree for fear of losing the love of his boss, business associates and social set. He expressed it privately by promiscuity and solitary drinking. These activities were compulsive reactions to situations in which he overtly submitted to a man but wished to defy him. For example, he would accept orders from the boss with complete obedience, but feel rebellious and hostile and on the verge of attacking the boss. He would then go out and indulge in alcoholism and promiscuous sexuality. Once the boss invited him to play golf. He dared not refuse, accepted graciously, but cursed himself violently for complying. His sexuality was compulsive and indulged in under the influence of alcohol, so that he wished to be cured of these episodes. He had no personal interest in these women, who were almost impersonal agents for indulging his sexuality. In fact he was potent with them only when under the influence of alcohol. He too showed very clearly later in the analysis his rage when his receptive wishes were not satisfied.

Both of these patients were chronically pessimistic, anxious, and mildly depressed. They tried to escape by recourse to alcohol and promiscuity, although they were really very inhibited sexually. Drinking and promiscuity were to them symbols of defying conventions, and means of escaping from dependence and submissiveness, and resulted in feelings of deep guilt and anxiety. When in the country, away from women, bosses, and obligations,

both were much relieved. The psychoanalytic material showed that both struggled against strong wishes to be in second place, passive, submissive, dependent, and that both were in a chronic state of hostile rebellion against these wishes, since their pride demanded that they be first—independent, at the top. Hence their chronic defiance and hostility to bosses. This passive dependent trend was seen in their strong oral attachments to their mothers, and in their feminine identification with the women who were their sexual partners. Every attempt at intercourse resulted in acute anxiety. From childhood they felt intense guilt about sex. The parents had great expectations for their futures and they were driven by high ambition, but at the same time resented this drive and longed to give it up, be cared for, escape. Marriage was from duty and both rebelled against it. In both analyses the siblings were almost never mentioned or alluded to, so strong was the hostile rivalry with them and the oral attachment to the mother. A number of their early dreams were almost identical, namely dreams of being in a sexual situation with a woman and being seen by a man with consequent anxiety, and dreams of being inhibited in doing something. These dreams reflect the inhibition of the masculinity by the submissiveness to the father, which therefore causes much anxiety in the dreams, and is so fought against in life. Both men showed clearly the oral dependence on the mother and the masochistic passive submission to the father, and then the unsuccessful abortive efforts at hostile rebellion and defiance against the submissiveness. Mr. B.'s definance found greater outlet since he actually could indulge the alcoholism and promiscuity, which Mr. A. wished to do but could not because of anxiety. It may be significant therefore that Mr. B.'s blood pressure was more fluctuant and averaged lower than Mr. A.'s. Both male patients were masculine looking, tried to use sexual promiscuity and alcoholism as outlets and showed the chronic unexpressed rebelliousness particularly in relation to their bosses. Both showed well developed positive Oedipus complexes as well as the negative, *i.e.* masculine competition with the father as well as submission to him.

Another male patient, seen only in a few interviews, presented a psychological picture strikingly similar to these two. He was mild-mannered and submissive. He was strongly attached to his mother in an oral form as was seen by his indulgence in periodic candy jags. His rage from rebellion against his own submissiveness, and oral dependence, and from thwarting of these wishes, was expressed early in life by temper tantrums, which lasted until after adolescence. Threatened with loss of love because of them, he succeeded in controlling them and became milder in personality. Within a year after suppressing them his blood pressure rose from normal on repeated examinations, to 160 over 100 and went slightly higher during the next decade. Physical examination was negative. This case shows clearly the importance of the oral trend and how suppression of rage was followed by increased external mildness of manner and submissiveness, and by the development of essential hypertension. Compare Alexander's case report, pp. 139–152.

Miss C. was in her thirties, unusually quiet and charming. In her own words, she had "retired in favor of" (*8*) her mother and sisters. She felt that they were so much more attractive that she could not compete with them and she never had a single date until her middle thirties. She then began going with a

man her own age, and just when the affair threatened to become serious, her blood pressure, hitherto normal on repeated tests, rose sharply to more than 200 systolic over 130 diastolic. (Compare with Mr. A. whose hypertension increased when his anxiety blocked his attempts at sexual intercourse.) She had had no sexual experience. She gave up men and stayed close to her mother to whom she took an oral dependent attitude, as shown in her dreams as well as in life. The mother was the strong, dominating personality of the family and the patient had no one else upon whom to depend for love, having relinquished men. The patient was of fine type, gentle, and conventional with a strong sense of duty and obligation. She was the only one of the patients whose rebellion against her submission to her mother and to her conscience was not very largely conscious. For example, she went off on a trip, but could no more feel free than she did at home, like Mr. A. Thus she was the most inhibited patient of the series and her blood pressure was the highest. This greater repression may have been due to her father's violent death in a probably purposive accident. This intimidated her and increased her dependence upon her mother. As an example of her submissiveness in the transference, she once thought the analyst had suggested that she do something that she did not want to do. She felt compelled to obey although she hated to (like Mr. B. when the boss invited him to play golf) and wept with impotent rage at her inability to resist complying, due chiefly to fear of loss of love.

Miss D., a patient of Miller's, like Miss C., consciously retired in favor of her sisters. She was in her early twenties, quiet and sweet in manner and expression. Her blood pressure ranged from 150 to 180 systolic over 80 to 110 diastolic and was of at least three years' standing. She was the breadwinner for the family, working to support them and to send her sisters to college. She spent most of her time at home in an oral relationship to the mother who fed and cared for her when she returned from work in the evening, as though she were the man of the family. She had many unsatisfied dreams of being fed by the mother. Like the other patients, she was overly generous to those dependent upon her and pleasant and gentle in personality with a sense of duty so great that she was over-working and sacrificing her own life in order to contribute to the family. But she had constantly to control a conscious bitter rebellion against her submission to her mother, to her boss (a man) and to her own conscience which forced her to relinquish pleasure, sex, and independence, in favor of excessive work. She had temper tantrums especially against her boss which she barely succeeded in concealing. This consciously controlled defiance of the boss was exactly like the two male patients.

Two other patients in connection with whom less complete psychoanalytic data were available, were women. Miss M., a patient of Grinker's, was about thirty, with an essential hypertension averaging 175/100. Most characteristic of her was her naiveté and the fact that she never got angry. In this case, too, the mother was the dominant member of the family and ran the family, and the patient formed a strong predominantly maternal superego. She felt she ought to have the mother close by, but always felt better when the mother was away. The patient had had no sexual relations, and very few social relations with boys, and still did not know where babies came from. The extreme repression of the heterosexuality seen in the other cases, especially of the women, is also conspicuous here.

However, in this case, as far as was apparent after several months of analysis, the hostility seemed to be due less to rebellion against the submissive attachment to the mother, than to oral thwarting by the mother, *i.e.*, to anger at the mother for not satisfying all of the patient's demands upon her.

A mild fluctuating hypertension, frequently reaching 150/100, was found during the analysis of Miss O., a patient of MacDonald's. She was married, with two children, and developed anginal pains, panic and mild agoraphobia when her younger sister came to live with her. As in all the preceding cases, a dominating mother was prominent in the history and in the psychoanalysis. She sought constant approval from the mother, catered to her, had many oral demands upon her for care and attention, and also, largely in defence, death wishes toward her and sexual wishes for men which for a period developed into nymphomania, with demands for intercourse many times a day. Her psychoanalytic material was unusually overt. Thus the drainage of her hostility and her protest against the attachment to her mother was relatively successful, although at the cost of agoraphobia, nymphomania, and considerable disorganization of her personality.

The patients who showed the same conflict situation, but whose protest was comparatively successful and whose hostilities and sexuality were freer, showed some, but much lower, hypertension. A study is now in progress of the psychological correlations with the rises of blood pressure in these cases in which the pressure is normal some of the time.

IV. Controls

It is clear that dominating parents are common and that the conflict described is a general one and is not peculiar to cases of essential hypertension. However, pending further study of these and many more cases, the present material suggests that the *status* of the conflict may be peculiar to cases of essential hypertension. These patients submit, but they stifle intense hostility which is near to consciousness. As controls, it is easy to observe patients without hypertension who have this same conflict situation but who solve it in other ways. For example, one patient shunned situations in which his submissiveness would be stimulated, by doing independent free lance work, saying frankly that he was unable to work for a boss. He relieved unavoidable tensions by gambling in which he indulged with very little conflict. In other cases, the submission is accepted with very little protest or with some narcissistic compensation. A comparison has not yet been made of the psychology found in essential hypertension with that found in angina and in the cardiac arhythmias. The first impression is that the hostilities in the latter cases are freer, as seen in the dreams. In a small series of eight controls, I have not found hypertension in patients who have the same conflict as the hypertensives but who have workable solutions for it. Thus, so far as the control series has been examined, no essential hypertension has been found in cases in which 1) the submissiveness is accepted, 2) the problem is avoided by shunning submissive situations, 3) the rebellion and hostility are adequately repressed and bound by organized neuroses or find adequate outlets in life behavior or sexual activity by assuming forms which are not too conflictful and anxiety producing for the individual, or, *possibly* 4) the hostility does not arise from this protest situation, but from another source, for example, direct oral thwarting, but this is questionable.

V. Status of the Hostilities

The following was the status of the hostilities in the cases studied: The hostility was 1) intense and 2) chronic. However gentle the exterior, the analyses made it clear that these individuals were chronically boiling with rage.[1] 3) The hostility was in all these cases the central issue of the analysis, the pathogenetic element so to speak. 4) The psychological level of the hostility may be of importance since in all these cases it was close to consciousness. There is reason to suspect that the crucial point here may be the proximity of the hostilities to motility. 5) The hostility was in all cases very inhibited. On the surface these individuals were non-hostile and even overly gentle, but did not lack energy. They worked, in fact often overworked, and succeeded, while protesting against doing so. The hostility found no adequate outlet in behavior in life, through drainage by sexual activity (which often discharges unconscious sadistic impulses) or even in dreams, although there was apt to be considerable conscious hostile fantasy. 6) Although inhibited, the hostility in these cases was not adequately bound in an organized chronic neurosis, for example, paranoia, compulsion neurosis, chronic alcoholism, etc. Cases have been reported by Draper (*3*) and Eisler (*6*) in which the hypertension disappeared when the patient developed neurotic symptoms. The hostility was never adequately expressed but never relinquished. The regressive wishes to give up the struggle and accept a passive dependent emotional situation were also not accepted. Both were blocked.

[1] One patient reported the following dream: "I heard the hissing of steam all around me and then realized it was within myself. I became tense and trembling with the pressure. An elderly woman called me 'the boss'. But I said: No, that man is the boss". In his associations the patient brought out his rebellion against his boss and against the analyst, and to the steam associated a machine trembling with the pressure of steam within. This pressure was his rebellious hostility against the boss and the analyst, chronic and unvented.

VI. The Common Psychological Features

Surveying these seven cases grossly, the following similarities are conspicuous. The first is the prominence of the conflict with a dominating parent, especially the mother. This was central in every case, but in that of Mr. B. the father also dominated the patient. Two main reactions were seen in the patients. The one was a submissiveness to the mother, transferred in part in the male patients to the father, thus producing in all cases a submissive situation against which the patient was in constant hostile, unsuccessful rebellion. This rebellion when it broke through took the form in the two men of promiscuity and alcoholism, and in the women of sexual wishes which were overtly indulged only by Miss O. In these few cases, those with the freer outlets had lower blood pressure levels. The other main reaction to the mother, prominent in all cases, was the oral dependent attachment to her which formed part of the submissiveness and was rebelled against, but which, when not satisfied, due to both external thwarting and internal inhibition (guilt, pride, ambition, and narcissism) lead to chronic rage at the frustration, and was a component of the alcoholism. The oral material and the anger from unsatisfied oral wishes were conspicuous in the material of all the cases.[2] In the case of Miss M. the hostility from thwarted oral wishes to the mother was the main theme, and the component of

[2] This checks with Karl Menninger's statement that it is common to find in the histories of essential hypertensives that in childhood they have been thrust prematurely into situations of self-reliance (*10*).

rebellion against the mother attachment not so important as in the other cases, at least so far as the analysis had progressed in several months. (It may be that hostile rebellion against the mother will appear later in the analysis.)

The second similarity was the repression of the heterosexuality with attempts to indulge it despite anxiety. Mr. A., after his compulsive attempts at sexual freedom, wished to give up heterosexuality entirely because it caused him so much conflict and anxiety. Mr. B. had no interest in the women with whom he was promiscuous, and usually never saw them before or afterwards. They were only part of the bouts of alcoholism and promiscuity which relieved the tensions from rebellion against his boss. In contrast is an anginal patient without hypertension. He was of the Don Juan type with real appreciation of feminine charms, found great pleasure in his relations with women, and could freely indulge his sexuality. The three women with the high blood pressures were strikingly similar in their repression of sexuality. Thus Miss C. never even had a date until she was past thirty. Miss D. had a very rare date, as a duty, at the behest of her mother. Miss M., nearly thirty, claimed such innocence of sexuality that she did not know where babies came from. In contrast was Miss O. When her impulses broke through she made excessive sexual demands. But her blood pressure only irregularly rose above normal.

The third similarity was in the status of the hostilities, as already described.

Other similarities are less definite. All of these patients were "nice" persons, as has often been noted. The reason for this has not been worked out. Probably it is due to a combination of the guilt and submissiveness. In general it seems especially difficult for essential hypertensives to come for psychoanalysis, probably because of their guilt and their fear of the oral and submissive wishes.

In all cases, the problem was a very deeply ingrained and repressed one, intimately organized into the whole personality. Whether or not the progressive rise in the level about which the blood pressure fluctuates is connected with progressive organization of the personality into a less flexible form, and what the interrelationships are, is a question of great theoretical as well as practical importance. The therapeutic aspect of it is discussed in Alexander's paper. Probably once the pressure ceases to return to normal levels in its fluctuations, both psychological and physiological therapy becomes more difficult. However, our observations indicate that psychoanalytic treatment has at least some effect in reducing or arresting the progress of the hypertension in these cases, but it is too early to draw definite conclusions as to the therapeutic results.

VII. Comment

As stated at the outset, this communication is a report of the preliminary phase of this study. Many essential problems remain untackled and unsolved. An important problem at this point is whether the essential hypertension is connected with hostilities from *any* source, such as oral thwarting, depending only upon their intensity, and status, or whether the conflict situation found in these cases is an essential part of the picture.

Another important question is that of the rôle of the anxiety. The hostilities have been examined thus far without special attention to their direction and relationships. It may be that the hypertension is most directly con-

nected with fear, particularly of the conscience.

The rôles of the heterosexuality and of the oral demands are also not worked out.

Two other approaches are promising. The one is a study of the psychological material in connection with the fluctuations in blood pressure, and in connection with the level about which the pressure fluctuates. Such correlations are reported in Alexander's paper and are being studied in the other cases. Some of the records contain daily blood pressure recordings and analytic material, over periods of several years. In one case, Mr. A., the level of fluctuation clearly fell after two months of psychoanalysis, as the patient accepted and enjoyed the passive situation. But after another six months, when it became conflictful, the level rose, and was high for nearly a year during intense hostile transference.

The other approach is that of a "microscopic" study of the dreams as done by French (7). This technique reveals elements not otherwise discernible. A lead is the impression of French that the proximity of the hostilities to motility may be critical.

VIII. Summary

An attempt is made to describe the common psychological features in seven cases of essential hypertension. The prominent similarities are 1) the prominence in every case of a dominating mother, with submissiveness and oral dependence toward her, transferred in the cases of the two men to their fathers; with consequent chronic, hostile, unsuccessful, nearly conscious rebellion against the submissiveness, and chronic unexpressed rage at unsatisfied oral demands and at independent activity and work; 2) marked inhibition of heterosexuality, although indulged to some extent despite anxiety; 3) the status of the hostilities—intense, chronic, inhibited, near to consciousness and perhaps to motility, not adequately expressed, and not adequately repressed and bound as by an organized neurosis; 4) the inability to accept and satisfy either the passive dependent wishes or the hostile impulses, so that these individuals were neither weak and dependent nor aggressively hostile, but were blocked in both directions. During periods when either trend was more satisfied, the blood pressure was markedly lower.

These results are more than suggestive but the series is too small as yet to establish conclusively whether or not these psychological features are generally typical for cases of essential hypertension.

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BLOOD PRESSURE FINDINGS IN RELATION TO INHIBITED AGGRESSIONS IN PSYCHOTICS

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THE STUDY of the psychopathology of repressed hostilities in relation to essential hypertension by Franz Alexander and his collaborators, suggested to me the possibility of finding elevated blood pressure in two groups of psychotics where there is a high degree of repressed hostility: 1) the depressed group who are self-accusatory and turn the hostility against themselves, and 2) the paranoid group who defend themselves against their hostility by accusing others of aggressive tendencies toward them. Altogether 193 psychotic patients were studied. Initially a group of 116 psychotics were studied: 60 paranoid, 33 depressed, and 23 schizophrenics. A second group of 77 cases in which the blood pressure was predicted on the basis of psychological examination before being taken, was used as a control and will be discussed later.

REVIEW OF LITERATURE

One finds numerous contradictory reports of both high and low blood pressures in the various mental disorders. None of the following workers gave adequate statistics or adequate psychological descriptions of the patients and of their predominant emotional state at the time when the blood pressure was taken. M. Craig (*5*) found low blood pressure in cases of patients with excitement and high pressure in those with depression. In women with "acute melancholia" he found an average pressure of 150 mm. systolic, in men slightly lower. Excited patients ranged from 95 to 110 mm. H. Alexander (*3*) in "A Few Observations on the Blood Pressure in Mental Diseases", found elevated blood pressure in "melancholia"; he found somewhat higher readings in acute mania than Craig reports. Longworth (*16*) found no constant modification of blood pressure in maniacal and melancholic states in other mental disorders. W. R. Dunton (*6*) arrived at similar conclusions, again however without any correlation with the emotional states of the patients. John Turner (*19*) does not agree with the above findings. S. Clark (*4*) found no characteristic change in average blood pressure in mania or melancholia and no constant alteration with recovery unless recovery was accompanied by marked improvement in general health. Systolic blood pressure

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rose after acute excitement in a manner comparable to that of normal individuals after exercise. Sometimes he found a fall due to fatigue. He felt that finer purposeless movements of the chronic "maniac" or of agitated melancholia did not influence blood pressure. He makes this statement: "Any changes in mental or emotional state alone unaccompanied by marked restlessness or energetic motor activity as a rule did not influence the average blood pressure but occasionally a small rise was observed". His observations and those of Turner coincide in their statement that there was no relation between various forms of mental disorders and blood pressure except in cases of congenital deficiency.

M. C. Hawley, (*13*) without giving case material, concluded that the blood and pulse pressure become raised and are more marked as the restlessness becomes more marked. He found low blood pressures in stuporous cases. The pressure in manic cases was higher than in depressions while in melancholia the pressure was relatively high in patients in middle life. C. J. Enebuske (*7*) in discussing manic cases concluded that the blood pressure is higher than 150 mm. (which he considers the normal level). After the disease has run its course the tension is then around 150 mm. In manic attacks the pressure may rise to 210 or 250 mm. He found that "maniac" cases in young persons have a higher pressure than depressives of the same age but that the latter may develop hypertension values over 150 mm. He noted low blood pressure in catatonia and that some cases of dementia praecox may run a consistently high pressure of 210 to 320 mm. or a consistently low pressure from 90 to 110. He concluded that the elevations are due to 1) presence of vasomotor irritant in the blood producing contraction of peripheral arteries, 2) psychogenic causes such as "false ideas, visual and auditory hallucinations, commands, psychomotor impulses, hypervigilance, strained attention and efforts of will". The author does not give case histories nor discuss the emotional states of the patients. H. Freeman (*8*) found consistently low blood pressure in a prolonged study of 50 schizophrenics.

From the foregoing account we see that a number of workers have reported considerable elevation in other groups besides acute excitements. These observations have hitherto received no satisfactory explanation. However, N. Reider (*17*) in a study of the reactions of the blood pressure in psychiatric cases to the cold pressor test, cites three case histories and mentions the connection between repressed aggressions and blood pressure elevation.

Method

The emotional state of each case was determined by a personal interview with the patient before taking the blood pressure, and by the attendants' or nurses' observations. A study of the patient's record also was made. The interview was usually brief and was an attempt to get a dynamic view of the patient's illness by encouraging the patient to discuss his ideas in his own words. Usually leading questions were confined to such remarks as, "Can you tell me why you are in the hospital?" . . . "What is your opinion as to the reasons for your illness?" Specific stimulus words and attempts to stimulate the patients were avoided. Each interview included a question as to the patient's own reactions to his illness and to the hospital environment. The blood pressure was determined with a standard mercury sphygmomanometer after a period of rest in bed (in most cases) and the average taken of 5 con-

secutive readings. The physical condition of all patients was noted from the record of the examination. No cases were accepted in this study where there was any evidence of heart disease, arteriosclerosis, renal or any other organic factor which might influence the blood pressure. In all cases urine and Wassermann examinations were negative. In this study care was taken to avoid measuring the blood pressure of psychotic individuals who showed transient emotional flareups. Instead, patients were selected in their typical emotional states which had been persisting for some time. A list of suggested patients with various types of emotional disturbances was obtained from the physicians and attendants. Then many of these patients were selected for the study after they were seen by the writer in their typical emotional attitude. Many of the cases displayed the same attitudes weeks and months later. It is a generally accepted fact that in patients with essential hypertension but without mental diseases, the emotional reactions to the doctor influence the blood pressure. In this study special care was taken to avoid such emotional reactions.

It was possible to subdivide the paranoid and depressed psychotics into three groups for each division. The predominant trends were ascertained from an interview with the patient, from the attendants' and nurses' observations, and from a careful study of the history with particular attention to content. The dynamic concept of inhibited aggressions is fully described by Alexander (*2*) in this symposium and does not need further elaboration here except to state that the paranoid defends himself against his own hostility by accusing someone else of the aggressive tendencies. In the Paranoids, classification was based on the following criteria:

Paranoids

Group I.—Irritability, anger, suspiciousness, and well organized persecutory delusions, with intense affect.

Group II.—Clear-cut reduction of the same affective expressions with a certain amount of complacency.

Group III.—Grandiose megalomanic trend, affording a high degree of narcissistic satisfaction.

It was also possible to classify the Depressions into three groups, as follows:

Depressions

Group I.—Expression of extreme self-deprivation, self-accusation, tension, and obvious severe depression with considerable anxiety and fear.

Group II.—Hypochondria, moderate tenseness, some anxiety and restlessness, and sadness but to a less degree than in Group I.

Group III.—Retardation of speech and motion, little ideation; also the stereotyped "crying jag" in which masochistic attitudes are obviously highly erotized. Also characteristic passive, complaining attitudes, showing little fight in relation to the illness—literally "giving up". Hypochondria.

Examples of each type in the Paranoids and Depressed groups follow.

Paranoid I, Case #21, a man of 39, blood pressure 162/113, showed marked distrust of the doctors, the barbers, his relatives and others, in a typically paranoid manner. As shown in his case history as well as present attitudes, his aggressions toward those around him were projected, and therefore constantly stimulated his fears and gave him an apparent excuse to express resentment and anger. In the interview he was suspicious, irritable, evasive, tense and tremulous. He had a bad taste in his mouth, he said, because his sister put poison in the food. He was sarcastic and angry at the physicians in the receiving hospital who com-

mitted him to the State Hospital. He said, "They said I drank and beat my wife. I never drank in my life".

The attendant's observations are as follows: "He is seclusive and hallucinates. He complains of trouble with his digestion (delusion of being poisoned) and constantly wants to go home. He does not give his right name and complains that the attendants annoy him. He is always trying to make a good impression and insisting there is nothing wrong with him".

A brief abstract of his history reveals the following facts: His work is sporadic, consisting of a series of failures in attempting to earn a living. Twelve days before admission he jumped out of a window and ran through the rain to his sister's house. He waved a crucifix and prayed and talked to Jesus, then ran through the house thinking that someone was going to poison him by gas. He thought all of his family were against him, even his mother, and that people were surrounding the house in order to kill him. He heard men's and women's voices but could not remember what they said. It is interesting to note that a second examination a week later showed no change in his emotional state or blood pressure—his average blood pressure was 160/105.

An example of Paranoid II, is the following: Case #13, a young man of 26, who is tense, somewhat suspicious, ill at ease, and constantly fidgets with his hands. He says spontaneously, "I had several shocks. I lost some money by pickpocketing and robbery. That was just after a nervous experience I had at the city hall when I had to serve on a jury. That gave me a shock. I had planned to go to college. Strange people were acting in a queer way and looking at me peculiarly".

The attendant's observations are: "The patient is quite cooperative but extremely tense and nervous. He is a good worker and gets along fairly well with others".

He was admitted for observation in 1931 because he had been acting strangely, following heat exhaustion a year previous. In 1937 he became irritable, seclusive and antisocial, and showed fear, tension, apprehension and evasiveness. About 8 months before admission he became angry at his parents and walked out in the rain in his best clothes. His history discloses that for years he had been fearful, apprehensive, seclusive, and suspicious—thinking other people talked about him. Shortly before admission he attacked his sister with a knife. He was admitted voluntarily because he was afraid he would harm someone. The average blood pressure at the time of the writer's examination of him was 145/91.

An example of Paranoid III:—#16. This 30-year-old woman says, "I am Christ". She claims that she can read the doctors' minds, and that the superintendent of the hospital communicates with her by radio, to tell her that she is going home. The patient was the third of five children; she was always jealous of the others and felt that she was being discriminated against by her family. She felt superior to most people and in the hospital claims she is another person, a superman. She thinks she has sexual powers of both man and woman. She maintains a superior attitude in the hospital. Her average blood pressure is 127/90. Such patients as this have regressed to a megalomanic state in which their conflicts have reached a partial solution and their aggressions are not continually being stimulated.

In the depressed patients the intensity of the repressed hostilities was determined by the evidence of self-accusatory ideas and guilt which indicate the presence of unconscious aggressions that are turned inward

against the individual, a familiar psychoanalytic concept (*1*). The amount of tension accompanying self-accusations seems to measure the strength of the hostility which is repressed. These factors, rather than any other, are from the dynamic point of view found to be diagnostic of an intense depressed state. It was occasionally found, for example, that while a patient may be classified as depressed from the hospital diagnosis which is usually made a few weeks after admission, a close scrutiny of the patient's emotional state years later might reveal on the one hand a marked withdrawal of the patient from the environment similar to a schizophrenic state, or on the other hand a matter-of-fact adjustment to somatic delusions unaccompanied by any affect. An example of a depressed patient with intense repressed hostility producing marked guilt is as follows:

Depressed I, Case #63: This patient is a young woman of thirty, a college graduate, who had been rather moody during the last four years since the appearance of an inactive goitre. After the death of her roommate at college some months ago, who died as a result of an operation for carcinoma of the breast, the patient has talked about her continuously. She has become increasingly depressed, feels that she is dying and going to hell, that she has committed too many sinful sexual acts and so abused her body that God will never forgive her. She feels that she is paying for the sins of everyone because she denied God and has expressed the wish to crack her own head open with a knife or hatchet". The blood pressure was 153/91.

Another example of considerable self-accusation with hostility turned inward is case #81. She is a 47-year-old married woman who has been depressed for several years. Her statement is "I killed myself. I blame myself for everything I have done. I hope they don't put it in the papers. I hear mother's voice saying you will still be sorry. Everything I eat makes me sick. I know they don't want me at home. Wherever I go everybody looks at me. I don't look right". The blood pressure was 148/103.

An example of Depressed II, is #77, a 45-year-old woman who is cooperative and seems rather passive, sad and dejected. After the blood pressure was taken she was a little tearful. Her blood pressure at admission in July, 1937, was 120/80. Three weeks later, at the time of the examination by the writer, the average pressure was 140/105. She had been depressed since her mother's death 5 years previously. She complained that she had failed to mix with people all of her life. Her mother's death was a great blow to her because they had always been together. The father had died before the patient was born. Increasing irritability toward her husband and increasing depression after the mother's death resulted in frenzied scratching of her body and frequent crying spells. After about 2 weeks in the hospital there was some improvement in the marked restlessness and crying.

Depressed III:—Occasionally one finds depressed patients like Case #116 who have a low blood pressure (100/80). At first glance his blood pressure reading would seem to contradict our theory, but a closer study of the case reveals a psychological state which can be correlated with the blood pressure. The patient is a 27-year-old unmarried man who for the past 2 years has had fluctuating depressions and excited, grandiose episodes. The present illness followed an expansive period of several months' duration in which he felt that he had an unusual capacity to make large amounts of money and entered into foolish grandiose financial

operations in which he ran up huge bills, etc. In previous hospitalizations he has been euphoric, irritable, hyperactive and talkative. From his history it appears that his mood changes followed difficulties in jobs or business reverses. His record reveals that he never had any real interest in girls, that he chided his married brothers for their marriages, was passive and slow and showed a lack of initiative. An attack of gonorrhea a year ago gave him much concern. Six months before the present admission he lost his job and for the next four months lay in bed and refused to talk to anyone. Just as suddenly a few weeks before admission he became alert, overactive and grandiose. As he is observed on the ward he appears to be extremely passive, deeply preoccupied, somewhat sad in appearance and has little to say. He is not agitated or tense, he is docile, does what he is told by the attendants, sleeps quite well but has a poor appetite. About all he says in response to questions is that he wants to go home. He has no idea of what may be wrong with him. One gets the impression that this patient has given up the battle and is getting considerable satisfaction from hospitalization. He has advanced to a state in his psychosis in which he has renounced competition, withdrawn interest in reality and is getting satisfaction from a rich fantasy life. There is more than a little resemblance to the catatonic reaction here. Although the pros and cons of diagnosis in this case could be discussed at length, from the dynamic point of view there is no question that his emotional state is one in which there is a "hibernation" so that he undergoes relatively little stimulation of the hostilities against which he is protecting himself. In other words the patient seems to have "given up" psychologically for the time being, and in this way avoids his conflicts.

A different type of regression in the depressed emotional state (Depression III) is illustrated in Case #83. This is a woman of 48 who has been hospitalized for several years. Her constant complaint is that she has no bones in her body, has no nerves and is unable to account for the fact that she exists. She is unusually pleasant, passive and cooperative. The attendant, who has known her during her entire stay describes a "rutlike" pattern in which the patient is rather quiet, passive and withdrawn. She often laughs and talks about her ideas. There is evidently little conflict over her hostilities which have become diffused and generalized. She indulges in a relatively meaningless expression of somatic delusions which seem to be a partial solution of her conflict. Her blood pressure is low.

In contrast with the more acute emotional disturbances of depressions and paranoia, a group of relatively withdrawn schizophrenics was studied. As has been noted by numerous authors (Freud (*11*), Tausk (*18*), etc.), in this psychosis conflicts are avoided by means of a marked withdrawal of the ego from painful reality and a return to a relatively early infantile state, the narcissistic state.

Not only the schizophrenics but the other types of cases as illustrated by the above examples, showed a lower blood pressure when a fair solution of the conflicts was achieved. As was to be expected from the foregoing considerations the blood pressure was below normal in the majority of schizophrenic cases. This finding of course has been noted in the literature beginning with the work of Kraepelin (*14*) and by the group working at the Worcester State Hospital (*10*) etc., but no dynamic psychological explanation has hitherto been offered. In the narcissistic stage of withdrawal from reality there is little frustration and conse-

quent diminution or absence of stimulation of hostilities. This would suggest a reason for the "unresponsiveness of the sympathetic system", as expressed by Gottlieb (*12*). This state could be compared to that of a hibernating animal whose cardiovascular system does not have to respond to rage reactions. Nolan Lewis's (*15*) findings of hypoplasia in the aorta of dementia praecox patients suggests some connection with the fact that the load on the cardiovascular system has been greatly reduced in these deep states of regression. The slow circulation time (Freeman (*9*)) might also be explained on the same basis.

Examples of Blood Pressure Correlation with Chronic Emotional States

It is obvious that the blood pressure will fluctuate depending on the state of the emotions so that the same individual may show a range of fluctuation. In this study some observations of blood pressure and emotional state were made over a period of several weeks by the writer. A number of cases were found in which the history showed a record of observations of blood pressure over a period of years. When these were correlated with the emotional states as noted also in the history, one could see considerable fluctuation of pressure, varying directly with the emotion. It is obvious that not much can be concluded from single blood pressure observations, nevertheless even these show striking correlation with the emotional states of patients over a period of years. Those observations taken in 1937 were made by the writer and are the average of five readings.

For example:

Case #1 admission

8/34 blood pressure 105/75 passive, cooperative

11/25/35 blood pressure 130/80 passive, daydreams a lot

5/22/36 blood pressure 126/80 continues passive

6/1/37 blood pressure 150/100 tense, sullen, angry, irritable, complains of family persecuting him

6/17/37 blood pressure 130/86 passive, cooperative, smiles in silly fashion

Case #27

1928 blood pressure 125/60 emotional state not recorded

2/34 blood pressure 120/80 pleasant, cooperative

8/24/34 blood pressure 170/90 hears voices; hears a boy talking to her; thinks her son was killed

1/5/36 blood pressure 144/80 somewhat irritable

9/15/37 blood pressure 180/103 tense, angry, intense delusions of persecution

On the other hand, in Case #37, a depressed man, whose blood pressure was taken several times at different intervals, at each examination the emotional state was approximately the same, and so was the blood pressure.

(examined by the writer)

5/31/37	blood pressure	144/90	depressed
6/ 8/37	" "	143/100	"
6/17/37	" "	136/ 93	"

In order to test the validity of the hypothesis concerning the relation between repressed aggressions and blood pressure, a control experiment was undertaken. A prediction of the blood pressure was made after an interview was held with the patient in order to determine the state of his hostile emotions. The predicted blood pressure and the classification of the emotional status according to the groups outlined were noted on a card. Then the actual blood pressure was taken and checked by another observer. Depressed and paranoid patients were classified into three groups for each disease. The same criteria were used as already described.

The lower limit of predicted blood pressure for the first Paranoid Group was arbitrarily set at 150/100. In the second group the predicted range was 120 to 150 systolic and 80 to 90 diastolic. Under 120/80 was the range used for the third group of predictions.

The following tables will show the

results of the predictions as well as the average blood pressure findings in the original group studied.

INITIAL STUDY OF HYPERTENSION IN PSYCHOTICS

PARANOIDS

Age 20–30

Case No.	Age	Sex	Delusions of Persecution	Megalomania	Group	Blood Pressure (average of 5 readings)
1.	24	f	+	−	I	150/100
2.	28	f	+	−	I	138/104
3.	21	m	+	−	I	161/ 82
4.	28	m	+	−	II	135/ 90
5.	27	f	+	−	I	161/ 90
6.	29	m	+	−	II	145/ 90
7.	27	f	+	−	II	140/ 86
8.	27	m	+	−	II	139/ 84
9.	25	m	+	−	I	159/ 98
10.	27	m	+	−	I	154/102
11.	26	m	+	−	I	134/102
12.	25	m	+	−	III	127/ 87
13.	26	m	+	−	I	145/ 91
14.	22	f	+	−	I	142/ 96
Age 30–40						
15.	32	f	−	−	II	140/ 80
16.	30	f	−	+	II	127/ 90
17.	33	f	−	+	II	120/ 85
18.	33	f	−	−	II	122/ 90
19.	36	f	+	−	I	125/100
20.	37	f	−	+	II	122/ 89
21.	39	m	+	−	I	162/113
22.	32	m	−	−	III	110/ 80
23.	32	f	+	−	I	140/100
24.	37	m	+	−	I	158/103
25.	39	f	+	−	I	145/ 95
26.	30	f	+	−	I	153/101
27.	37	f	+	−	I	180/103
28.	39	f	+	−	I	144/ 93
29.	33	f	+	−	I	148/102
30.	38	f	+	+	II	147/ 91
31.	32	m	−	+	III	120/ 86
32.	38	f	+	+	III	134/ 82
33.	37	f	+	+	III	128/ 83
34.	38	f	+	+	II	134/ 95
35.	38	f	+	−	I	172/ 99
36.	34	f	−	+	II	134/ 87
37.	31	m	+	−	I	158/101
38.	33	f	−	+	III	120/ 85
39.	34	m	+	−	I	134/103
40.	40	m	+	−	II	133/ 94
41.	47	m	+	+	II	146/ 86
42.	47	m	−	−	II	137/ 91
43.	40	f	+	−	I	156/ 92
44.	47	f	+	−	II	148/ 85
45.	40	f	+	−	I	156/ 96
46.	44	f	+	−	I	134/103
47.	40	f	+	−	II	145/ 92
48.	41	f	+	−	I	159/ 97
49.	43	m	+	−	I	186/112
50.	49	m	+	−	I	182/110

PARANOIDS—Continued

Age 40–50

Case No.	Age	Sex	Delusions of Persecution	Megalomania	Group	Bloood Pressure (average of 5 readings)
51.	40	f	+	−	II	140/ 97
52.	49	f	+	−	I	166/101
53.	41	m	+	−	II	107/ 79
54.	41	f	−	−	II	145/ 86
55.	43	f	+	−	I	197/114
Age 50–60						
56.	52	f	+	−	I	155/ 89
57.	52	f	+	−	I	160/ 85
58.	50	m	+	−	I	159/ 96
59.	51	f	+	−	I	150/ 99
60.	60	m	+	−	I	145/ 80

DEPRESSIONS

Age 20–30

Case No.	Age	Sex	Self Accus.	Tense	Somatic Delusions	Guilt	Passive Regression	Group	Blood Pressure
61.	22	m	+	+	−	+	−	I	146/ 80
62.	25	m	+	+	−	+	−	I	140/ 91
63.	29	f	+	+	−	+	−	I	153/ 91
116.	27	m	−	−	−	−	+	III	110/ 80
Age 30–40									
64.	30	f	+	+	−	+	−	I	145/ 90
65.	34	f	+	+	+	+	−	I	182/117
66.	35	f	+	+	−	+	−	I	135/102
67.	37	m	+	+	−	+	−	I	143/100
68.	37	f	+	+	−	+	−	I	137/101
69.	38	f	+	+	−	+	−	II	131/ 95
Age 40–50									
70.	40	f	+	+	+	+	−	II	142/ 99
71.	40	f	−	−	−	−	+	III	121/ 93
72.	40	f	−	−	−	−	+	III	110/ 77
73.	42	f	+	+	−	+	−	I	142/100
74.	42	m	+	+	−	+	−	I	139/ 90
75.	44	f	+	+	−	+	−	I	144/100
76.	44	f	−	−	−	−	+	III	124/ 80
77.	45	f	+	+	+	+	−	II	140/105
78.	46	f	+	+	−	+	−	I	148/ 98
79.	49	f	+	+	−	+	−	I	191/102
80.	49	f	−	−	−	−	+	III	105/ 78
81.	47	f	+	+	−	+	−	I	148/103
82.	41	f*	−	−	+	−	+	II	138/ 91
83.	48	f	−	−	+	−	+	III	113/ 80
84.	41	f	+	+	−	+	−	II	139/ 86
Age 50–60									
85.	52	f	+	+	−	+	−	I	157/104
86.	52	f	+	+	−	+	−	I	210/114
87.	53	f	−	−	−	−	+	III	96/ 73
88.	55	f	−	−	−	−	+	III	100/ 60
89.	57	f	+	+	−	+	−	I	195/112
90.	58	f	+	+	+	+	−	II	158/ 94
91.	60	f	+	−	−	+	+	II	140/ 85
92.	60	f	+	+	−	+	−	I	160/107

* Negress.

Schizophrenics (All regressed, passive)

Case No.	Age	Blood Pressure
Age 20–30		
93.	25	116/88
94.	23	121/89
95.	26	122/87
96.	23	122/89
Age 30–40		
97.	37	125/93
98.	33	106/82
99.	38	122/83
100.	35	104/59
101.	37	116/90
102.	38	127/88
103.	37	113/80
104.	30	121/80
105.	30	110/90
106.	32	119/60
107.	36	99/36
108.	37	77/55
109.	37	117/88
110.	36	111/86
111.	31	113/80
112.	32	99/80
113.	30	110/90
114.	34	126/75
Age 40–50		
115.	41	99/75

Control Study

Classification	Case No.	Predicted B.P.	Observed B.P. (Average of 5)
Paranoid I	118	above 150	117/80
	119		110/90
	120		155/109
	121		154/80
	122		168/89
	123		158/90
	124		163/94
	125		168/107
	126		138/84
	127		205/115
	128		177/88
Paranoid II	129	120 to 150	142/82
	130		157/87
	131		155/91
	132		145/87
	133		101/78
	134		140/82
	135		147/89
	136		138/82
	137		123/79
	138		119/79
	139		144/76
	140		126/73
	141		137/88
	142		130/98
	143		132/90
	144		132/83
Paranoid III	145	below 120	97/70
	146		110/80
	147		107/74
	148		133/91
	149		107/74
	150		94/75
	151		110/76
	152		114/77

Control Study—Continued

Classification	Case No.	Predicted B.P.	Observed B.P. (Average of 5)
Depressed I	153	above 150	165/105
	154		170/92
	155		122/80
	156		172/112
	157		124/70
	158		158/100
	159		163/80
	160		168/112
	161		177/105
	162		120/84
	163		162/116
	164		162/100
Depressed II	165	120 to 150	128/83
	166		143/109
	167		113/90
	168		130/80
	169		126/80
	170		99/80
	171		131/90
	172		125/75
	173		167/114
	174		97/70
	175		123/82
Depressed III	176	below 120	109/72
	177		118/90
	178		134/86
	179		138/85
	180		95/60
	181		110/76
	182		97/79
	183		113/83
	184		116/80
	185		112/86
	186		113/70
	187		110/70
	188		107/71
	189		110/80
	190		100/76
	191		92/75
	192		105/80
	193		123/84
	194		96/70

Predictions of Blood Pressure in Psychotic Patients on Basis of Estimation of Repressed Hostility (Systolic)

Classification	No. of Cases	No. Correctly Predicted	% Correctly Predicted
Paranoid I (above 150)	11	8	72.7%
Paranoid II (120–150)	16	12	75%
Paranoid III (below 120)	8	7	87%
Depressed I (above 150)	12	9	75%
Depressed II (120–150)	11	7	63.6%
Depressed III (below 120)	19	16	84.4%
	77	57	74%

Average Blood Pressures

Classification	Original Study No. of Cases	Original Study Av. B.P.	Controls No. of Cases	Controls Av. B.P.	Total No. of Cases	Total Av. B.P.
Paranoid I	34	155/95	11	155/93	45	155/94.5
Paranoid II	20	136/88	16	135/84	36	135.5/86
Paranoid III	6	118/83	8	109/77	14	113/79
Depressed I	18	157/100	12	155/96	30	156/98
Depressed II	7	141/93	11	126/86	18	132/88.7
Depressed III	8	110/78	19	110/77	27	110/77
Schizophrenics	23	112/79				

Discussion of the Tables: In discussing the results of the predictions of blood pressures in the various groups, it is pertinent to ask whether or not the accuracy is higher than might be arrived at by chance. With the help of a statistician, Dr. M. W. Richardson, of the Department of Psychology at the University of Chicago, it was shown that the correlations are much higher than chance would warrant.

An estimate was made of the standard error of the systolic blood pressure in the original study and in the predicted cases, for the three group classifications—the differences between the means of the group classifications are clearly within the accepted level of statistical significance. Thus, for example, the standard error for the average finding of 155 mm. of systolic pressure in the original and the control Paranoid I group is 1.0. The standard error for Group II in the Paranoid series was 1.3 for the initial study and 1.4 for the controls. The standard error of the difference between the average systolic blood pressure of Groups I and II is 1.7. This includes the predicted group. The remainder shows similar close correlations.

In the control group of the 11 individuals who, from the clinical examination of the emotional status, belong to the group of Paranoid I, 72.7 per cent are correctly placed in the systolic blood pressure category. This percentage is to be compared with 28.6 of the total paranoid individuals falling in this class, that is, a prediction of 150 mm. systolic or over. The essential or correct prediction over chance is 44 per cent, with a standard error of 13. This figure, then, becomes highly significant since 44 per cent is over three times the standard error. In the second group of paranoid individuals it is plus or minus 9.8. The excess over chance in this group is four times the standard error. In the third group of Paranoids, the standard error is plus or minus 4.

In the depressions the excess percentage of correct cases is a little less than three times the standard error, and in the third group, that is, Depressed III, the excess is five times the standard error.

It will be noted that there is a much higher correct prediction rate when systolic pressure only is used as an indication. Predictions had also been made on the basis of diastolic pressures but it was found that the percentage of correct predictions showed a great deal of variation and that it was impossible to make consistently correct predictions. The findings seem to indicate that there is a functional correlation between the emotional status and the systolic pressure.

It was possible to subdivide the depressed and paranoid patients into three groups according to the intensity of the emotion as already outlined. It will be noted, however, that fewer successes in predictions were made in Group I Paranoids and in Group II Depressed. Actually it is quite difficult sometimes to distinguish a depression of moderate degree from an intense depression because of the fact that external manifestations may be rather similar. Further study is needed to work out more exact criteria for differentiation.

From the empirical observation of the patients' emotional states a classification was made into three groups which were correlated with the blood pressure. The interpretation was made that it is the state of the repressed aggressions which is the main factor in stimulating the blood pressure elevations. Of course it is possible that anxiety may also be a factor in producing blood pressure elevation, but this anxiety probably is connected with repressed aggressions.

In the 193 cases studied there appears to be a significant correlation between the repressed hostile emotion and the degree of elevation of blood pressure. The study suggests that where there is a chronic psychological tension arising out of chronic inhibited hostile impulses, chronic elevation of blood pressure may result. Further studies of similar groups continued over a long period of time are needed to show the extent of variations and fluctuations of the blood pressures of psychotics. It is suggested that in psychotics with an intense degree of repressed aggression, permanent damage to the cardiovascular system occurs as a result of long sustained hypertension (*2*). Conversely, those patients with a high degree of passive regression throw little strain on the cardiovascular system. It would appear from the above findings that the study of the blood pressure of a psychotic individual could be utilized in a practical way. For example, if an active paranoid or depressed patient's blood pressure drops considerably it would be a good indication that a considerable amount of regression is taking place and that the patient is making a passive infantile adjustment to the hospital. On the other hand, a rising blood pressure in a paranoid patient might be a danger signal of an impending disturbed state. Similarly an elevated or rising pressure in a depressed patient would be a warning that the repressed hostilities are being directed inward and that a suicidal danger is present.

Summary

A study of the correlation between the emotional status and the blood pressure of 193 psychotic individuals was made. A significant degree of correlation was found. It is possible to divide both paranoid and depressed psychotic individuals into three groups on the basis of a clinical examination of their emotional status. This offers a ready and convenient estimate of the dynamic state of the emotions in these groups. The blood pressure findings may be significant in diagnosis and prognosis.

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SYMPOSIUM ON HYPERTENSION

EMOTIONAL FACTORS IN ESSENTIAL HYPERTENSION

PRESENTATION OF A TENTATIVE HYPOTHESIS

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THE VIEW PRESENTED in the following is an attempt to integrate a number of diversified observations of clinical, pathological, physiological and psychological nature, into a consistent etiological picture of essential hypertension.[1] These etiological conclusions do not claim final validity and should serve merely as a basis for further systematic studies which may lead finally to an etiologically founded therapeutic procedure. Speaking of essential hypertension, I refer to the clinical condition, which is defined in the article of Katz and Leiter, in this symposium, a clinical condition consisting of a chronic elevation of the sytolic and diastolic blood pressure which can not be retraced as a secondary result to known pathological changes in the kidneys, the vascular system, or other organs.

Since in other articles of this symposium, the somatic aspects have been dealt with extensively, I shall restrict myself only to a brief summary.

The Clinical Course: Perhaps of greatest importance for the problem of etiology is the typical course of hypertensive disease. In most cases one can differentiate an early phase in which the blood pressure shows great fluctuations and a later phase, in which the blood pressure becomes stabilized on a higher level. This was most convincingly demonstrated by Fahrenkamp (*5*). It can be validly suspected that in this initial period the blood pressure temporarily may return to normal or fluctuate around the normal level and for shorter or longer periods around a higher level. Further thorough observations over a longer period of time of such incipient cases, would be of greatest importance in order to establish the primary causes.[2] Only in the second irreversible phase does the blood pressure become stabilized at a high level. This typical course of essential hypertension makes the assumption improbable that degenerative changes in the blood vessels are the primary causative factors. The first fluctuating phase seems to be definitely a functional one.

Pathological Findings: This assumption is favored by the conclusion of most authors that organic findings such as left ventricle hypertrophy, pathological changes in the large vessels and in the arterioles when present in cases of essential hypertension, should be considered rather the result than the cause of hypertension because they rarely can be found in early cases.

Physiology: In discussing the prob-

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[1] In this article no extensive references to literature are made, since the literature is reviewed separately in this issue by E. Weiss.

[2] In the Chicago Institute for Psychoanalysis at present we are engaged in such a clinical investigation.

lem of etiology, it is important to differentiate between mechanisms and causes. It is generally accepted that the chronic elevation of the blood pressure is the result of an increased tonus of the arterioles. Vaso-constriction in the splanchnic area, because of the vast blood capacity of this region, probably contributes most to the elevation of the blood pressure. As causes of this chronic increase of tonus, different possibilities are considered, none of them established with certainty. The increased tonus may be the result of stimulation of the vasomotor centers. This is the neurogenic theory. It may be the effect of pressor substances in the blood stream; this is the humoral theory. For this latter some experimental evidence has been furnished lately by Harry Goldblatt (*7*) who artificially produced hypertension of longer duration in dogs by creating local ischemia of the kidneys by clamping of the renal arteries. He assumes that due to this ischemia a pressor substance is retained which however has only a pressor effect in combination with cortical adrenal hormone. Of course the neurogenic and the humoral theories are not contradictory. Both mechanisms may be at work.

It is obvious that neither of these explanations answers the question of etiology proper. They concern merely intermediary mechanisms. The etiological problem is: What is the cause of the chronic vasomotor stimulation, or if the humoral theory is correct, what is the cause of the renal ischemia responsible for the retention of pressor substances?

As has been mentioned before, the typical clinical course of hypertensive cases, makes it seem improbable that in early cases generalized pathological changes in the blood vessels, or local pathology of the renal vascular system are causative of the renal ischemia. If local renal ischemia should turn out to be the intermediary cause of chronic hypertension, in the early phases of the disease, this ischemia must be due to a functional spasm of the renal vessels, rather than to irreversible histopathological changes. In any case if further investigations would corroborate the assumption that a vascular spasm resulting in renal ischemia is the intermediary cause of chronic hypertension, the essential etiological problem would still remain unsolved, namely, the origin of the local spasm of the renal vessels.

In the following the question of intermediary mechanisms—humoral or neurogenic—will be disregarded and I will concern myself merely with observations which might throw light on the primary causes of essential hypertension.

General Psychological Observations: A large majority of authors agree that the clinical manifestations of essential hypertension are greatly influenced by the emotional state of the patient. I mention only the observations of Goldscheider (*3*), O. Mueller (*16*), Mohr (*13*), Heyer (*9*), Moog and Schürer (*14*), Fahrenkamp (*5*), Alkan (*1*), Fishberg (*6*), Schultze and Schwab (*18*), Wolfe (*20*), Soma Weiss (*19*), Moschcowitz (*15*), Karl and William Menninger (*12*), Karl Menninger (*11*) and Lewis Hill (*10*). Ayman and Pratt (*2*), and Riseman and Weiss (*17*) emphasize the coincidence of neurotic personality traits with hypertension and K. Menninger suspects the importance of inhibited aggressive impulses. Also Hill mentions the rôle of inhibited hostile tendencies. Some of these authors observed that under acute emotional strains the blood pressure rises and remains elevated for a shorter or longer period. These elevations are usually superimposed upon an already heightened blood pressure. After the patient has calmed down again the blood pressure may drop but remain on a higher

level than normal, characteristic for the patient.

The influence of acute emotions upon the blood pressure has been also experimentally reproduced in animals by Cannon (*3*) and his co-workers under the influence of rage and fear. According to his experiments, elevation of the blood pressure is one constant element of a complex physiological syndrome characteristic for the emotional state of rage and fear. This syndrome (increased adrenalin production, mobilization of sugar, shortening of the clotting time of the blood, increased blood pressure) is a utilitarian reaction of the organism preparing it and making it fit for flight or fight.

Psychoanalytic Observations: The psychoanalytic study of cases as described in the previous articles of this symposium allows a more continuous comparison of chronic and not only of acute emotional states and blood pressure. Moreover, the psychoanalytic method makes possible a detailed evaluation of the psychological material. This offers an approach to the question of whether or not the emotions which influence the blood pressure are of a specific nature. The comparative study of a series of cases suffering from essential hypertension indicates that chronic, inhibited, aggressive hostile impulses, which always appear in connection with anxiety, have a specific influence upon the fluctuations of the blood pressure. Furthermore, it suggests that patients suffering from hypertension have a characteristic psychodynamic structure. This consists in a very pronounced conflict between passive, dependent, feminine, receptive tendencies and over-compensatory, competitive, aggressive hostile impulses which lead to fear and increase a flight from competition towards the passive dependent attitude.[3] This vicious circle in itself is, however, extremely common being the central emotional conflict of a large number of neurotic individuals who have normal blood pressure. Characteristic for the hypertensive patient is, however, his inability to relieve freely either one of the opposing tendencies: neither can he freely accept the passive dependent attitude or freely express his hostile impulses. A kind of emotional paralysis can be observed which results from the two opposing emotional attitudes blocking each other.

Confronting these psychological observations with the clinical, pathological and physiological facts and with the results of animal experiments, the following etiological assumptions can be made.

In normal animal life, fear and rage find their expression in physical flight or attack, for which the body prepares itself under the influence of these emotions. One important element of this preparation consists in the increased blood pressure. Human beings living in a competitive civilization are equally and perhaps even more permanently exposed to fear and hostile impulses, yet have much less opportunity to give expression to these feelings in physical combat. Social life requires an extreme control of these hostile impulses. A neurotic form of this control is unsuccessful attempts at repression. One of the best founded discoveries of psychoanalysis is that impulses which are inhibited in their expression sustain a chronic tension which is apt to have a permanent—or we may call it a tonic effect upon certain physiological functions. This is the etiological theory of the psychogenic organ neuroses. An acute elevation of the blood pressure is part of the normal reaction to acute rage and fear. Our assumption is that a *chronic* inhibited rage may lead to a *chronic* elevation of the blood pressure.

[3] See description of this conflict on page 143.

Such inhibited rage never finds its natural consummation in physical aggression which is followed by fatigue when the heightened blood pressure returns to normal. Such accumulated and never adequately expressed hostile aggressions are like a foreign body which is the source of a permanent irritation. The organism is constantly in preparation to fight. Typical of this state of apprehensive preparedness is a heightened blood pressure. Of course we know that these hostile impulses are not permanently at the same level. In the course of life, during contact with the environment, they become frequently stimulated; at other times they become repressed and retreat from the psychic surface into the deeper layers. This comes to expression in the fluctuations of the blood pressure.

According to this assumption, the typical course of essential hypertension might be described as follows: The maturing individual in the course of his life gradually becomes more and more confronted with the complex problems of maintaining his and his family's existence, his social position and prestige. In our present civilization all these tasks unavoidably involve hostile competitive feelings, create fears and require at the same time an extreme control of these hostile impulses. Those who through constitution or through early life experience have acquired a greater amount of inhibitions, will handle their aggressions less efficiently than others and will tend to repress them. On account of their inhibitions, they can not find socially acceptable, legitimate vents for their aggressive feelings, and thus these hostile impulses become accumulated and increase in intensity. It must also be borne in mind that the neurotic individuals who are more than normally blocked in relieving their hostilities and aggressions usually become inhibited also in many other respects, particularly in sexual expression. All these inhibitions make them, in their struggle for life, less effective, create feelings of inferiority in them, stimulate their envy and increase their hostile feelings toward their more successful, less inhibited competitors. These hostilities again require a greater amount of control and thus lead to greater inhibitions, greater inefficiency, and in turn again stimulate hostile, envious and competitive tendencies. This vicious circle is one of the best known mechanisms revealed by psychoanalytic study of neurotic personalities. Our experience is that the chronic hypertensives belong to this group of overly inhibited, yet at the same time, intensely hostile and aggressive individuals. Of course not all of these persons are necessarily hypertensives. The same neurotic conflict situation may find other entirely different expression. I refer to such well known clinical entities, as manic depressive states, compulsion neuroses, and paranoia, and criminal behavior.[4] It seems that essential hypertension develops when circumscribed neurotic symptoms which serve for the draining of pent-up hostile impulses are absent. This assumption is substantiated by such observations as that of George Draper (*4*) who observed the return of a long standing elevation of the blood pressure to the normal, coinciding with the patient's developing certain neurotic symptoms.

It is probable that in the first phase of this disturbance—when most cases

[4] It is noteworthy that depressed and paranoid patients in whom hostile impulses play such an important rôle, often show marked hypertension as has been described by Miller in this symposium. It seems that in many of these cases, the psychotic symptoms are insufficient to serve as a vent for the extremely strong, hostile impulses, characteristic for such patients.

are not yet under medical observation —these patients if studied would show in their everyday life a greater than normal degree of fluctuation and frequent transient elevations of their blood pressure. I assume that this instability of the vasomotor system is the expression of a specific psychoneurotic conflict situation, characterized by the inability to handle accumulated hostile impulses. The hostile impulses are neither thoroughly repressed nor adequately expressed. This psychological tension serves as a constant vasomotor stimulus and leads to a functional over-taxation of the circulatory system, which lasting over a long period may result in vascular changes, possibly in the first place in the renal vessels. These secondary vascular changes may account for the stabilization of the blood pressure on a high level. In this second phase the disturbance has become irreversible. Of course a constitutional vasomotor instability must be also considered. The familial nature of essential hypertension is well established.

Essentially this concept is not new. A number of authors have come to the same conclusion: namely, that essential hypertension is in its early phase a functional disturbance gradually leading to those pathological changes which are responsible for the irreversible stabilized malignant phase. Whereas Fishberg (*6*) and many other internists are chiefly impressed by the hereditary familial nature of the disturbance, others—like Riseman and Weiss (*17*), Ayman and Pratt (*2*), Alkan (*1*), and Wolfe (*20*) emphasize in addition to constitution also the etiological importance of psychic factors for the early phase of the abnormally fluctuating blood pressure. What our psychoanalytic observations add to this general psychogenic concept is a working hypothesis regarding the precise nature of the emotional factors. The affinity of hostile impulses to blood pressure elevation is well established by experiment. What is assumed, is that the excessive and inhibited hostile tendencies which are typical of hypertensives have a continued effect upon the blood-pressure-controlling physiological mechanisms, and through years may lead to permanent histological changes.

The question of heredity is then reduced to a more general problem. If it is true that the vasomotor instability is a manifestation of a psychoneurotic condition the question is to what degree this psychoneurotic condition should be considered as inherited or acquired.

Concerning this question the most interesting observations are those of Schultze and Schwab (*18*) who point out on the basis of extensive statistical studies that negroes in Africa very rarely suffer from chronic hypertension whereas negroes living in America show it in a very high percentage and supply a surprisingly large number of malignant cases. These observations indicate that—not the racial constitution—but different environmental and cultural conditions, are responsible for this frequency: namely the difficulties of adjusting to the new conditions of life which require an unusual amount of self-control. The difficulty of adjusting to the complex conditions of cultural life is the essence of psychoneurosis.

The undeniable fact that neurotic traits run in families does not necessarily require a hereditary explanation. Psychiatric experience shows that apart from heredity there is another perhaps even more common form of transmission of neurotic trends from generation to generation, namely through the psychological influence of neurotic parents upon their children.

Conclusions

We come to the conclusion that the early fluctuating phase of essential hypertension is the manifestation of a psychoneurotic condition based on excessive and inhibited hostile impulses. As such it is a reaction of the individual to the complexities of our present civilization. Since the same psychological condition is extremely widespread and finds expression in different forms of neuroses, the question of specificity still requires further investigation. The assumption of a constitutional instability of the vasomotor system therefore cannot be discarded. It is to be hoped however that further psychological investigations on hypertensives will make it possible to discriminate a specific neurotic handling of hostile impulses which necessarily leads to extreme fluctuations of the blood pressure and then secondarily to its later organic consequences.

The therapeutic possibilities of the psychoanalytic method in essential hypertension cannot be as yet conclusively formulated. It is obvious that in all those progressed cases in which one has to reckon with histopathological vascular changes one cannot hope that through psychotherapy the blood pressure can be brought back to a normal level. Of course also in these cases it is possible that the diminution of emotional conflicts may at least reduce the fluctuation superimposed upon a high average level. However psychotherapy has its greatest chances during the early fluctuating phase and therefore will have primarily a preventive value.

At present I must refrain from any definite therapeutic conclusions because most of our cases are still in the process of treatment. Some observations, however, made during the psychoanalytic treatment of such cases are quite encouraging, for example, that a patient during an emotionally calm period of several weeks' duration showed a definitely lower systolic and diastolic pressure and minimal fluctuations. Lewis Hill (*10*) reported a cessation of the hypertension in a case of a successfully analyzed patient.

Life seldom allows even emotionally well-balanced people to remain always calm and poised. Much less can it be expected that psychoneurotic individuals, to which the majority of the hypertensives seem to belong, even after successful treatment, will always be free from apprehensions and aggressions. Under the influence of their daily life they will show at least the same amount of emotional upsets as anybody else. If the assumption is correct that the hypertensives have a constitutionally less stable vasomotor system, these emotional fluctuations will necessarily come to expression in fluctuations of their blood pressure. What psychotherapy can hope for is a better emotional adjustment and as a result of this, less daily fluctuation of the blood pressure, that is to say, less taxation of the cardiovascular system. Thus, psychotherapy may prevent the development of those secondary organic changes which are probably responsible for the malignant stabilized forms of essential hypertension.

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RECENT ADVANCES IN THE PATHOGENESIS AND TREATMENT OF HYPERTENSION*—A Review

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PHYSICIANS WHO GRADUATED before the World War will remember the confusion surrounding the subject of hypertension and its relationship to kidney disease and arteriosclerosis. Richard Bright (*13*) had sought a reason for the hypertrophy of the heart which he found in so many of his patients with albuminous urine and diseased kidneys. He suspected an altered quality of the blood or an increase in the peripheral resistance. The celebrated paper by Gull and Sutton (*53*) in 1872 on "Arteriocapillary Fibrosis" called attention to "the morbid change in the arterioles and capillaries as the primary and essential condition of the morbid state called chronic Bright's disease with contracted kidneys". Clinical sphygmomanometry (Von Basch *113*) enabled Allbutt (*3*) in England, Huchard (*68*) in France and a little later Janeway (*70*) in America to make some noteworthy advances in the understanding of "non-renal" hypertension. Prior to their observations it was thought that arteriosclerosis was responsible for hypertension and that such patients would die of chronic kidney disease. Allbutt, especially, called attention to a large group of individuals in whom hypertension existed without any evidence of kidney disease, and this process, widespread in the civilized world, has come to be known as essential hypertension.

There is little need to emphasize the importance of hypertension. According to the statistics of the Metropolitan Life Insurance Company (*32*) every other individual in the United States past the age of 50 years dies of cardiovascular-renal disease. From other sources (*38*) we have evidence that probably half of these deaths are due to essential hypertension, that is, that almost one-quarter of all people past the age of 50 years die of the effects of hypertension on one or another of the vital organs. Thus essential hypertension becomes the gravest problem of middle adult life, not even excepting cancer (*61*).

America is rapidly becoming populated by people of advancing years. For example, in 1900 it was estimated that 20 per cent of the population fell in the age group 40–60, while in 1950 it is estimated that 30 per cent of the population will fall into this age group. This is the period when hypertension is most likely to manifest itself and to become the most important factor in the development of heart, blood vessel and kidney disease.

Hypertension enters into another important aspect of public health. It is only necessary to recognize "that the social consequences of chronic disease are masked in unemployment and de-

* The term "hypertension" in this article refers to essential hypertension.

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pendency" to realize that this is so (*90*). Since so much chronic disabling disease is found in the population on relief and since hypertension is one of the most important factors in the determination of this increasing chronic disability, hypertension is in reality a most important contributing factor to this undeveloped aspect of social security.

Pathogenesis

Race and Climate: Hypertension is a disorder largely confined to occidental civilization. There is a good deal of evidence to support this. Thus studies of African natives (*30*), the Chinese (*56*), Buddhist priests in Ceylon (*54*), and Egyptians of the laboring classes (*69*), all indicate that hypertension is very rare among these peoples. In this connection it also seems important that the blood pressure of foreigners living in China (*41*) and the tropics (*97*) are lower than when they are living in a temperate zone. Related to these questions come the important observations of Schulze and Schwab (*101*) who found the incidence of hypertension in the American southern negro two and a half times greater than that of the southern white. They and their associates (*102*) also showed that the tendency to hypertension, as determined by the Hines and Brown (*67*) ice water test, exists to a greater degree in the American southern negro. This bears on the question of heredity because it is acknowledged that the ancestors of these negroes could not have had hypertension since the negroes in Africa do not have it now. Thus it would seem that the American southern negro in his contact with our civilization over a period of 200 years must have acquired hypertension to an even greater degree than the white American. It is also interesting to know that hypertension runs a more severe course in the negro (Metropolitan Life Insurance statistics, *32*). So that we are presented at the outset of our discussion of constitutional and hereditary factors in the pathogenesis of hypertension with this extraordinary fact.

Constitution and Heredity: A review of recent progress in the pathogenesis of hypertension has been made easier by a comprehensive study by Sodeman (*106*) from which I shall take the liberty of quoting freely.

"Carefully controlled studies indicate that, in patients with essential hypertension, the familial incidence of vascular disease far exceeds that of patients suffering from other complaints. Family after family is reported with definite hereditary trends. Ayman made a direct study of the blood pressure in 1524 persons in 277 families. A tendency toward elevated blood pressure early in life was found in hypertensive families, a finding which was largely absent in members of normal families . . . Weitz tried to circumvent the difficulties of following many generations through the often inaccurate histories of the patient by studying the collateral family groups. These individuals were living and could be submitted to examination . . . Omitting the details of his analysis, his conclusions, that the predisposition to essential hypertension behaves in the majority of cases as a Mendelian dominant, might be quoted here. Ayman has described a personality type, both emotionally and physically hyperactive, not only in the patient with established hypertension, but also in certain of their children with mildly elevated blood-pressure readings. These findings he interprets to indicate the hereditary nature of the personality as well as of the blood pressure.

"Studies of identical twins subjected to the opposing strains of widely di-

vergent environmental factors confirm the above conclusions. Vascular reactions may be so similar in identical twins that capillary microscopy may be used as a means of establishing the diagnosis of their relationship".

Recent studies by Pearl (*89*) show a definite hereditary influence affecting the constitution of individuals with cardiovascular-renal disease. Hines (*67*) found a family history of hypertensive cardiovascular disease five times as frequent among persons who have hypertension or who are hyperreactors to a standard stimulus test (cold pressor test) as it is among persons who react normally to the test. In the study of twins and family groups he found that the type of reaction and blood-pressure test followed an inherited pattern. He concluded that it is probable that the trait is inherited as a dominant characteristic and that the hereditary factor plays an important rôle in the development of essential hypertension.

Peripheral Resistance

Before considering the vasospastic factors in the environment that apparently act to precipitate hypertension let us refer to the part played by the vegetative nervous system.

Medical lag required almost 25 years for the gradual acceptance of the idea that arteriolosclerosis is not the cause of hypertension but that it is the result. Hypertension persists and finally a diffuse hyperplastic sclerosis of the arterioles follows.[1] This clinical concept of a vasospastic disorder finally gained headway however and the question then became—what is responsible for the vasospasm that precedes the vascular disease. Here we come upon the question of the importance of the vegetative nervous system but first we must cite evidence for the presence of vasospasm. This is the factor that is held responsible for the increased peripheral resistance suspected by Richard Bright and still to-day the center of the controversy concerning the cause of essential hypertension. It has been generally acknowledged "that viscosity, blood volume and cardiac output do not differ significantly from normal in hypertension but that a distinct and marked increase in peripheral resistance especially in the arterioles is an invariable finding" (Sodeman *106*).

Nowhere can vasospasm be better seen than in the eye-grounds in hypertensive subjects. The most pronounced vasospasm is often seen in the so-called malignant hypertension (*72*) and in eclampsia (*48, 55, 60, 114*) in both of which states the blood pressure may be very high and followed by serious consequences to the cardiovascular renal system. Herrick's (*63, 64*) observations concerning the enormous incidence of hypertensive-vascular disease and chronic nephritis following the toxemia of pregnancy are of interest in this connection. In passing it may also be remarked that ophthalmoscopy has kept pace with other advances in the study of hypertensive-vascular disease and represents an integral part of the study of such patients. The ophthalmoscope is just as valuable an instrument in the study of the patient with hypertension, including eclampsia, as renal functional tests are to the patient with nephritis.

Sodeman (*106*) discusses the nature of peripheral resistance in hypertension in the following way.

"The control of peripheral resistance (arteriolar tone) in diastolic hypertension could be moderated through at least 3 mechanisms: nervous control, a local change, or hormonal or chemical substances. Studies in the nature of

[1] This question will be discussed again in connection with Goldblatt's work on experimental hypertension.

the peripheral resistance have been largely controversial until the recent work of Prinzmetal and Wilson in this country and of Pickering in England.

"*The Question of Nervous Control:* Prinzmetal and Wilson attacked the problem by the use of an apparatus to measure blood flow through the extremity. They first investigated the widespread theory that increased peripheral resistance in the splanchnic area alone was responsible for elevated arterial tension. If this were so, the normal cardiac output should produce a greater blood flow through the periphery in the hypertensive individual than in the normal person. No change in blood flow from the normal was noted in malignant, benign, and secondary hypertension, implying that the increased vascular resistance in hypertension is no greater in the splanchnic area than in the arm. The peripheral resistance is, therefore, generally elevated. This is in keeping with the histologic changes in the arterioles of voluntary muscle.

"Using the same technique, together with the application of heat and reactive hyperemia, these same authors were able to show that the vessels of hypertensive individuals were capable of dilatation and that the increased peripheral resistance is due to a generalized vascular hypertonus and not to primary changes in the blood-vessels.

"Having established the presence of generalized vascular spasm, these observers were concerned with the possible mechanisms of its production, as stated above. Three possibilities were obvious, nervous control through the vasomotor nerves, a local fault, or a chemical or hormonal influence. Their approach was directly upon the nervous theory because of the known influences of the vasomotor nerves on the diameter of arterioles and the level of the blood pressure. They reasoned that if the peripheral resistance in hypertension were dependent upon vasomotor stimulation one could assume that any procedure which would release vasomotor tone in a part would produce a greater blood flow through that part in hypertensives than in normal individuals. Using the same blood-flow technique, they produced vasomotor release by both heat and novocaine injection of nerves. Increases in blood flow under these circumstances were essentially the same in patients with benign, malignant, or secondary hypertension and in normal individuals. The results, then, failed to support the hypothesis of exaggerated vasomotor tone as the cause of hypertension.

"Pickering, working in England independently from Prinzmetal and Wilson, but using similar methods, reached similar conclusions. However, in the determination of the influence of the vasomotor nerves he used a calorimetric method to determine blood flow. The use of the latter technique is all the more important in that it confirms the results of the plethysmographic method that hypertension is not nervous in origin. . . .

"In essential hypertension, the results of these investigations indicate 'that normal vasomotor activity is superimposed on an intrinsic vascular hypertonus which is independent of the vasomotor nerves'. Vasomotor responses may affect the level of the blood pressure to a marked degree but that does 'not prove that the hypertonus of arterial hypertension is vasomotor in origin'. Pickering states that, as the Hines-Brown test shows, the vasomotor nerves remain active in hypertension. There is 'little doubt that vaso-constriction of nervous origin does constitute a considerable fraction of the peripheral resistance in persistent hypertension', as in normal in-

dividuals. But he contends further, from the above results, that it does not constitute the abnormal factor responsible for raised arterial pressure. He and Kissen were unable to confirm the Hines-Brown test. They obtained variable results, especially in their elderly control series and in patients with essential hypertension. The average size of the response was approximately the same in elderly subjects with normal blood pressure as in those suffering from essential hypertension.

"As convincing as the above evidence appears in establishing the fundamental nature of essential hypertension, it is not as yet fully accepted . . . To be sure, the mass of evidence in the literature lends credence to the nervous theory. However, as far as Sodeman has been able to determine, it is entirely equivocal. Prinzmetal and Wilson, in their search of the literature, also failed to find conclusive evidence to support the hypothesis of exaggerated vaso-constrictor tone. The marked drop in blood pressure attending spinal anesthesia and anterior root or splanchnic nerve section is, of course, compatible with the neurogenic theory and does indicate the profound influence of the nervous system on the arterioles, but in no wise proves the rôle of the nervous system as the fundamental cause of essential hypertension. The association of nervous and mental instability, and the relationship of the occurrence of essential hypertension to our complicated civilization are no more convincing. Although the evidence for non-nervous origin of essential hypertension is meager, it is clear-cut, to the point, and convincing".

The vasospastic effect of inhalation of tobacco smoke is of special interest from the standpoint of treatment in hypertension and this was made the subject of a preliminary report by Herrell and Cusick (*62*). They demonstrate the actual photographic results of vasospastic retinal changes caused by the inhalation of tobacco smoke. They consider this a part of generalized vasospasm and are of the opinion that it establishes beyond question the fact that tobacco plays a vasospastic rôle among some individuals. Other evidence of a similar nature has been contributed (*8*, *71*, *120*).

The Renal Origin of Hypertension

After struggling for 25 years to liberate ourselves from the idea that the kidney was responsible for hypertension we are being led right back to that concept by the experimental work of Goldblatt (*49*) and his associates. References to this work are made elsewhere in this symposium and in addition it is now so well known that we can briefly summarize rather than give it the amount of space which its importance deserves. This has been done very recently by Graybiel (*51*) as follows:

"It has been shown repeatedly that renal ischemia, produced by constricting the main renal arteries, as suggested by Goldblatt, will cause arterial hypertension. Experimental constriction of one renal artery results in temporary hypertension, and constriction of both results apparently in permanent hypertension. The amount of constriction determines the degree of hypertension. Thus slight constriction generally results in a benign form, usually without evidence of renal impairment; moderate or severe constriction results in a malignant form, with much renal impairment, and complete occlusion causes little or no rise in blood pressure. Many other methods which reduce the renal function and which have been recently tried do not result in a permanent increase in blood

pressure. Constriction of splenic and of femoral vessels has no effect on blood pressure.

"The exact mechanism whereby the kidney produces the rise in blood pressure in experimental hypertension is still unsolved, although it is the immediate result of the narrowing of the arterioles; the blood volume, blood viscosity and cardiac output remain normal. The problem thus appears to be the same as it is in essential hypertension. It was at first thought that the nervous system might play an essential rôle, with the reflex stimulation coming from the ischemic kidney. However, this does not seem likely, since denervation of the kidneys, section of the anterior nerve roots, total sympathectomy and denervation of the heart combined with total sympathectomy do not abolish the hypertension. Furthermore, it has been shown that constriction of the artery of a transplanted kidney, free from any possible nervous connections, leads to an increase in blood pressure.

"The results of Goldblatt's recent experiments, which were given in a preliminary report, suggested that the mechanism of this type of hypertension is primarily humoral and of renal origin. Thus, varying degrees of constriction of both main renal arteries are followed by hypertension while bilateral nephrectomy is not. This difference has been attributed to the absence of a hypothetic effective substance when the kidneys are absent. The constriction or occlusion of both renal arteries, when accompanied by occlusion of the renal veins, is not followed by the development of hypertension. This has been interpreted as being due to interference with the entrance of the hypothetic effective substance into the circulation. When hypertension is produced by constriction of one or both renal arteries, release of the constriction is followed, in a greater or lesser time, by return of the pressure to normal. Excision of the ischemic kidney at the height of the hypertension which follows constriction of one main renal artery is also followed by prompt return of the blood pressure to normal. It is interesting that Houssay, on the basis of transplantation of 'ischemic kidneys', also concluded that the ischemic kidney secretes substances that cause permanent arterial hypertension.

"Goldblatt has also carried out various experiments on the effect of partial and complete adrenalectomy, with and without supportive and substitution therapy, which have indicated that the adrenal cortex, but not the medulla, may play a significant rôle in this type of hypertension. The manner in which the adrenal cortex acts in this regard is as yet unknown; it may prepare the arteriolar musculature for the action of the hypothetic renal substance, or the reverse may be the case".

This is the first convincing demonstration experimentally of a disorder exactly similar to essential hypertension in man.

Now the question which interests us —if we are to compare this process to the problem of human hypertension— is this: is essential hypertension in man also due to renal ischemia and if so what is the mechanism? Perhaps there is some confirmation in recent pathologic studies which find the arterioles of the kidney involved to a much greater extent than are arterioles throughout the rest of the body, in patients with essential hypertension who have been studied at autopsy. Moreover it is a striking fact that although arteriolar disease occurs in the organs of individuals without hypertension it is almost never found in their kidneys while in hypertensive individuals, in addition to the vascular disease of other

organs, the kidneys almost never escape (*83*).

The problem is exactly the same as that which disturbed the medical world for so many years concerning the relationship of hypertension and arteriosclerosis except that it has been narrowed down to the kidney. As before stated it first was thought that arteriosclerosis caused hypertension and then finally we concluded that hypertension caused arteriosclerosis (diffuse hyperplastic sclerosis). For a number of years we enjoyed considerable security in this conclusion until the work of Goldblatt, cited above, led us right back to the renal origin of hypertension. And now the studies of Moritz and Oldt (*83*) raise the old question again—does hypertension result because of a primary renal arteriolosclerosis or is it that the renal arteries are peculiarly vulnerable to the effects of hypertension and hence show such a high incidence of arteriolosclerosis in hypertensive subjects. Moritz and Oldt believe the first and hence feel that their study lends pathological confirmation of Goldblatt's work so far as human hypertension is concerned.

Clinical confirmation also comes from the work of Homer Smith, Goldring (*18*, *103*, *104*) and their associates who employed diodrast, phenol red, and inulin clearances to determine renal blood flow in normal and hypertensive human subjects. They apparently demonstrate that there is a diminished renal blood flow in hypertensive subjects despite normal renal function. Furthermore the renal blood flow appears to be controlled predominantly by the efferent glomerular arterioles. This is commented upon elsewhere.

Finally some evidence for the renal origin of hypertension in man comes from a few cases (*12*, *16*, *44*, *76*) that have now been reported in which unilateral renal disease seems to have been responsible for hypertension—at least the hypertension has promptly disappeared when the diseased kidney has been removed.

Pressor Substances

Volhard (*111*, *112*) has long championed the idea of a circulating chemical or hormone as the cause of hypertension. He applied his theory to the concept of "pale" hypertension as distinguished from "red" (essential) hypertension. For many years he preached that the kidney was the central problem in hypertension but it was only with the convincing demonstration by Goldblatt that interest was revived in pressor substances in hypertension.

"Bohn confirmed the presence of a pressor substance in the blood of the 'pale' hypertensive, with negative results in the 'red' variety, as well as in normal individuals. Aitken and Wilson were unable to confirm the results of Bohn and ended in a criticism of his methods and results. Capps and his associates agree with Aitken and Wilson. Most of these experiments on circulating pressor substances have been carried out either by the introduction of extracts of the blood of affected individuals into animals and into animal preparations for physiologic tests for known pressor bodies, such as adrenalin and pituitrin, or by the transfusion to normal individuals or animals of the blood of hypertensive subjects. The results are confusing and often contradictory" (Sodeman *106*).

Renin: More significant observations regarding a pressor substance of renal origin have recently appeared. Tigerstedt and Bergmann (*109*) were the first to demonstrate in the normal kidney the presence of a pressor substance which they called renin. Their observations were confirmed and extended by other investigators (*10*, *59*,

65) who found that the pressor principle is thermolabile, is protein-like in nature, is limited to the renal cortex, and acts, over a prolonged time interval, either on blood vessels directly, or by way of the vasomotor nerves. A recent discussion of pressor substance in the cortex of the kidney by Friedman, Abramson and Marx (*47*) referred to the fact that extracts prepared from the ischemic kidneys of animals (with obstructed arterial blood flow to the kidneys) contained greater concentrations of pressor substances than the extracts of kidneys from control animals (*57*, *93*). Adopting a method of preparing the extract suggested by Harrison, Blalock, Mason and Williams (*58*) the authors attempted to investigate further the nature, mode and site of action of this substance. Their studies indicate that it has a local pressor effect upon the blood vessel itself. They call attention to the previous conclusion that the elevation of blood pressure both in hypertensive patients and in dogs with experimental hypertension following renal ischemia is caused by an increase in the peripheral resistance resulting from a generalized arteriolar hypertonus (*45*, *94*). According to this work the increased arteriolar tonus is not mediated by way of the sympathetic nervous system either in the experimental animal or in man. Hence the evidence is in favor of a chemical stimulus of renal origin, exerting a generalized pressor effect on the blood vessels, and being independent of the central nervous system. The renal pressor substance which the authors investigated appears to possess the properties compatible with and lending support to this view. Pickering and Prinzmetal (*91*) find a pressor substance in the cortex of many normal mammals which is not present in other tissues, which is not due to tissue autolysis or bacterial action and tests of which on unanaesthetized rabbits produced pressor effects. Merrill, Williams and Harrison (*82*) in a recent paper report that renal extract caused an increase in blood pressure, diminution in renal blood flow, swelling of the kidney and an increase in the excretion of urine. Their experiments suggest that the extract produces contraction of the efferent glomerular vessels.

This last interesting observation is in accord with the experiments on hypertensive man performed by Homer Smith, Goldring and associates, previously mentioned, whose observations also indicate that it may be the constrictor action of the efferent glomerular vessel which leads to diminished renal blood flow (*18*, *103*, *104*). All of our previous thinking has incriminated the afferent glomerular vessels.

Landis, Montgomery and Sparkman (*75*) present evidence that of many pressor substances studied, kidney extract, and protein-like material precipitated from such extracts, were the only ones which elevated blood pressure without decreasing peripheral blood flow, a relationship which is also characteristic of certain forms of human hypertension.

Endocrine Glands and Hypertension

In the vast majority of individuals with essential hypertension neither clinical nor post-mortem examination reveals any evidence of disease of the endocrine glands. However, a number of instances have been reported in which an endocrine origin seems certain as in cases of suprarenal tumor or basophilic adenoma of the pituitary. Even here we do not know whether it is the primarily involved endocrine gland or another gland of internal secretion which is reciprocally related that

causes the hypertension. Nor do we have definite knowledge as to how the disturbance in internal secretion brings about the hypertension.

Adrenals: It was long ago suggested (Vaquez (*110*)) that increased secretion of epinephrine was responsible for hypertension. He had observed the frequent coincidence of suprarenal hyperplasia and hypertension. There has been a great deal of discussion concerning this question but it was recently summarized by Rogoff and Marcus (*98*) who conclude that "existing experimental and clinical evidence is inadequate to support the view that epinephrine secretion is an important factor in the etiology and pathology of chronic hypertension". It is for this reason that they object to operations upon the adrenal glands in ordinary instances of hypertension. They also feel, and this question will be discussed later, that the same thing holds true for the hypophysis, that is, that there is no basis for intervention at the hypophysis in the treatment of hypertension. They refer to an editorial from the Journal of the American Medical Association (*37*) which states that "the therapeutic hazard in a disorder should not exceed the disease hazard".

Many instances have been described of adrenal tumors in association with hypertension. Labbé, Tinel and Doumer (*74*) reported a case of paroxysmal hypertension in association with a suprarenal tumor. This was proved by necropsy. Oppenheimer and Fishberg (*85*) collected 13 cases of suprarenal tumor with hypertension and added another with necropsy proof as well as a second in which the diagnosis seemed very probable. Since then a number of similar cases have been published.

Charles Mayo (*79*) reported the first case in which paroxysmal hypertension was cured by the removal of an adrenal tumor. Another such instance has been reported by Pincoffs (*92*). Donzelot (*31*) reviewed the subject of paroxysmal hypertension. Additional cases have been recorded since; one of the most recent by Binger and Craig (*11*) of the Mayo Clinic was discovered in the course of a sympathectomy for hypertension.

Pituitary: Cushing (*23*, *24*, *25*, *26*, *27*) described a remarkable clinical picture associated with basophilic adenoma of the pituitary in which arterial hypertension was a prominent symptom. Excessive secretion of the posterior lobe was held responsible and following the demonstration of such cases by Cushing and others the question naturally arose whether the pituitary played a part in the pathogenesis of essential hypertension in general. In the same regard Cushing (*27*) called attention to basophilic infiltration into the posterior lobe in eclampsia. Many investigators since however have been unable to correlate the basophilic infiltration with hypertension or eclampsia. Spark (*107*) has found basophilic invasion of the posterior pituitary very frequently in the absence of hypertension. Butt and Van Wart (*17*) were unable to correlate the basophilic infiltration with hypertension or eclampsia. Rasmussen (*95*) concluded that the relationship of the basophilic cells of the hypophysis to elevated blood pressure is far from proved. The sum total of evidence both clinical and experimental favors the latter viewpoint.

Gonads: Ever since the time of Huchard (*68*)[2] the association of hypertension with the menopause has been well known. In this connection it is important to differentiate the fluctuations of blood pressure, perhaps better referred to as the hypertensive state, from true essential hypertension that apparently is precipitated by the

[2] See pages 1, 74 in Reference (*68*).

menopause. Marked disturbances in vasomotor regulation of course occur at the menopause and it is entirely possible that the climacteric fluctuations in blood pressure are closely related to these disturbances. The supposed reduction of hypertension at the menopause due to theelin therapy (*100*) suggest studies of hormone excretion in hypertensive patients. Kylin (*73*) demonstrated a remarkable parallelism between the amount of gonadotropic principle excreted in the urine and the height of the blood pressure. But Scarf and Israel (*99*) were unable to confirm these findings.

Summary of Pathogenesis

A consideration of the material just presented indicates that hypertension is a constitutional disorder in which both hereditary and environmental (vasospastic) factors are important.

In an attempt to assign a proper relationship to the three systems of the body and to the various factors that play a part in the pathogenesis of hypertension a scheme has been constructed as shown in the accompanying diagram. This makes an effort to indicate the relative importance of constitutional and hereditary factors—which make up the base of the pyramid—with regard to the interrelated systems of the body that have to do with hypertension—shown as the sides of the pyramid. These systems are then shown as triangles with the sides of the triangles representing interrelated factors.

Material concerning the rôle of the psyche in the pathogenesis of hypertension has been reserved for the section on treatment where both considerations can be presented together.

Treatment

Drugs: Of the countless preparations that have been used in the treatment of hypertension none has received any particular consideration recently except sodium and potassium thiocyanate. Interest in this drug was revived by Westphal and Blum (*118*) after its use had long before been given up because of toxic reactions. Ayman (*7*) made a careful study of the use of the drug in hypertension and concluded

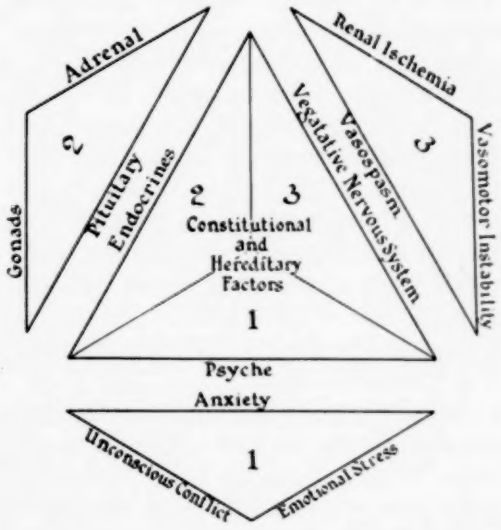

Diagram to summarize discussion of pathogenesis. The base of the pyramid is made up of constitutional and hereditary factors; the sides consist of interrelated systems which are shown separately as triangles with their sides representing interrelated factors.

that its hypotensive effect is closely associated with a toxic effect. For this reason he held its use impracticable. A little later Barker (*9*) reported satisfactory results in the control of the blood pressure level without toxic effects by maintaining blood cyanate levels of 8–12 mg. per 100 cubic centimeters. He reported that toxicity begins to appear when the blood level reaches 15–30 mg. "The cyanates may reach hazardous concentrations very quickly in some individuals, so that the administration of the thiocyanates is believed to be dangerous unless controlled by close observation and blood cyanate determinations". Griffith and

Lindauer (*52*) also obtained satisfactory results in a small group of patients by controlling the blood level of cyanates and devised a new micromethod for the determination of the blood level. Apparently, as with surgery, the thiocyanates act best in those cases in which vasospasm rather than arteriolosclerosis is the predominant feature of the clinical picture. This question will be discussed in connection with the surgical management of hypertension. It would seem that if the only object in the treatment of hypertension is to lower the blood pressure level thiocyanates will accomplish it in some patients. Just how it does so has not been determined. Suggestions have been made that it is by an effect on the blood viscosity although the general opinion is that viscosity levels in hypertension do not differ significantly from normal (*14*).

Surgery: Again and again we read in papers dealing with the surgical treatment of hypertension that "since the medical treatment of hypertension has failed surgery is justified". I question the failure of medical treatment; our attitude here will depend upon our objective. This will be discussed in the next section.

The writing of this section has been facilitated by a comprehensive review by Martin (*78*), just published. He cites the early work which formed the basis for a rapidly growing interest in the surgical treatment of hypertension. Recent trends in America and abroad may be classified under three types of operation: rhizotomy, adrenalectomy and sympathectomy.

At first interested in rhizotomy, the Mayo group (*1*, *5*, *19*) Adson, Craig and others, now perform subdiaphragmatic, extraperitoneal bilateral resection of the splanchnic nerves and a removal of the upper two lumbar ganglia with the intervening chain. This procedure, they believe, completely denervates the splanchnic vessels, the adrenal glands, and the kidneys. The Mayo group are still impressed by the hypersensitivity of the vasomotor mechanism in hypertensive people and the purpose of their operation, therefore, is "to dilate the splanchnic vessels, to decrease the liberation of epinephrine and to increase the renal blood supply". They have been concerned especially with the problem of the proper selection of cases for surgical care and have instituted hourly blood pressure readings for 24 hours with the patient at bed rest; have noted the effects of sodium pentothal given intravenously, and of sodium amytal and sodium nitrate given orally; and have studied the effects of spinal anaesthesia and the administration of avertin. If the blood pressure decreases to normal or nearly normal as a result of all these measures, the patient may be considered a satisfactory candidate for operation. Sequelae of their operation may be the loss of sweating on the feet and lower legs, permanent increase of the skin temperature on the lower extremities, paralysis of the ejaculatory powers due to weakness of the muscles of the urogenital trigone, and sterility in the male without loss of the libido. There is no alteration in menstruation or in childbearing function, and no sphincteric disturbance occurs in either sex. "In general, about 70 per cent of the entire group of patients were benefited clinically" (*20*). Allen and Adson (*4*) recently attempted to answer some current objections to the surgical treatment of hypertension. They are not convinced that essential hypertension in man is the counterpart of the experimental hypertension produced in animals by renal ischemia. Nor are they prepared to accept the evidence cited by Prinzmetal and Wilson con-

cerning the relative insignificance of vasomotor control in hypertension. Replying to some of the objections raised in a critical paper by Soma Weiss (*117*) they feel that there is no clinical evidence to indicate that those parts of the body not influenced directly by sympathectomy, as the heart and brain, may suffer a diminished blood flow after sphanchnic dilation. They realize that surgical results have not yet withstood the test of adequate time but they have been sufficiently encouraged to insist that the surgical treatment of hypertension deserves unbiased consideration and further trial.

Splanchnic nerve resection was first suggested in 1923 by Danielopolu (*28*). The two largest American series are those of Peet (*42*, *43*, *46*) and the Mayo Clinic. Peet was the first to do a bilateral intrathoracic resection of the splanchnic nerves for hypertension and the series from his clinic now totals more than 400 cases. He is greatly impressed by Goldblatt's work and believes that results in his human cases have been due to the fact that sympathectomy removes the "nervous clamp" from the renal vessels.

A comparison of the results of section of the anterior spinal nerve roots with sympathectomy (Peet's technique) has recently been published by Page (*86*) who has worked with Heuer at the New York Hospital. Twenty patients were subjected to section of the anterior spinal nerve roots and nine cases to resection of the splanchnic nerve and the lower thoracic ganglions. He states that while resection of the splanchnic nerves produces many of the effects that are observed after section of the anterior roots, they are often more transient. However, from the point of view of technical ease and lack of dangerous complications it is to be preferred. Page thinks that surgery in the treatment of hypertension is still in the experimental stage. In the series of 20 patients upon whom the section of the anterior spinal nerve roots was performed serious accidents occurred in 3; one patient died shortly after closure of the dura; another died from streptococcic meningitis; and a third patient developed transverse myelitis. Page feels that two of these accidents could probably have been avoided while the third, transverse myelitis, still remains a serious hazard.

Crile has been one of the most enthusiastic supporters of the surgical treatment of hypertension. His operation is a bilateral celiac ganglionectomy the results of which in 233 cases he has recently summarized in a book on the subject (*21*). The mortality rate of the operation itself "when thoroughly mastered" is 2.8 per cent. He finds the blood pressure to be reduced to normal in 17 per cent, 12 months after the operation, and partial or complete symptomatic relief in 87 per cent of the cases.

On the assumption (evidence against which has just previously been cited) that hypertension is the result of overactivity of the adrenal glands, the partial removal of the normal organs has been practiced especially by various foreign surgeons, mainly French (*77*). Fortunately the procedure has not been practiced extensively in America (*29*) as there is no experimental evidence to support it and an occasional evil result of surgical intervention has been reported (*37*, *105*). Adrenalectomies, adrenals denervations and the application of x-rays over the pituitary and adrenal areas (*22*) seem to me unwise tampering with vital tissues.

Very recently Goldblatt made some observations on the surgical treatment of hypertension (*50*). He states "it is also noteworthy that only the originators of each operation have been enthusiastic about the beneficial effects

of their operation and have reported poor success or failure with other methods. As in the case of other methods of treatment, factors other than the level of the blood pressure, such as disappearance of headache, and other subjective symptoms have been used in the evaluation of the effect of the treatment. The unreliability of such criteria need not be stressed. It is a striking fact that no matter what the type of surgical operation on the nervous system, the percentage of cases in which a significant lowering of the blood pressure has been reported is about the same for all. After all the operations the percentage of cases in which there is a return of the blood pressure to normal is relatively small".

Goldblatt suggests "that one obvious surgical therapeutic procedure is the possible improvement of blood supply to the functioning components of the kidney by increasing the collateral circulation". Such an operation would be somewhat comparable to the attempts that have been made to improve the blood supply to the heart muscle. He thinks there is probably more justification on an experimental basis for attempting such an operation than there has been for some of the surgical procedures that have already been practiced.

In completing our surgical observations we must not forget that just recently cases have been reported of unilateral kidney disease with hypertension in which the hypertension has subsided after the surgical removal of the diseased kidney (*12*, *16*, *44*, *76*). Together with an occasional example of adrenal tumor apparently responsible for paroxsymal hypertension it at least calls attention to the clinical necessity of studying the kidneys and the kidney regions very carefully even in what are considered ordinary instances of hypertension.

Certainly one of the strangest and most unscientific remarks that constantly recurs in all the literature dealing with the surgical treatment of hypertension is that "in so many cases although the level of blood pressure has not been influenced the patients have been improved". This means that headache, dizziness, fatigue and other symptoms have disappeared or are not so prominent but everybody who has had any experience with hypertension knows that the same thing can be accomplished with placebos.

Quite aside from this, some remarkable results have been reported in the apparent abolishment of hypertension and improvement of ophthalmoscopic findings. Similar things do happen however without surgery. The whole subject is a most difficult one to evaluate and I think the burden of proof is on the surgeons to show that patients operated upon live longer, suffer fewer complications, and above all lead happier and more efficient lives than those not operated upon. This will take prolonged observation of a large series of patients.

Psychic Factors in Hypertension

It is generally admitted that psychic factors play an important part in essential hypertension. Thus it is always emphasized that we must allow for the emotional element in the individual blood pressure reading and it is also well known that rest and reassurance play a large part in the medical management of hypertension patients both in relief of symptoms and in reduction of the blood pressure level. The early symptoms of hypertension are often psychoneurotic and the relation of emotional stress to the onset of hypertension and to aggravation of blood pressure are well known. So far as cause is concerned, however, the pre-

vailing view is probably as expressed by Fishberg (*40*), "in all probability, emotional and mental strains play purely an accessory rôle in the genesis of essential hypertension, serving to precipitate or aggravate the increase in blood pressure in those individuals who have the inherited constitutional predisposition". . . .

But a more fundamental rôle has been suggested by many authors. One of the first was Moschcowitz (*84*) who described a certain type of person, conforming to certain physical and psychic complexes, in whom hypertension is very likely to occur. Ayman (*6, 7*) observed symptomatic improvement as a result of simple suggestion in 82 per cent of patients with early essential hypertension and holds that the early symptoms associated with the disease are of psychic origin. Dissatisfied with the indefinite methods of reporting studies he insists that all studies reporting attempts at therapy in essential hypertension should present the following facts in the individual case: 1) age, sex and known duration of the hypertension; 2) the number of years of recorded hypertension; 3) observations of the fundi, heart and kidneys; 4) the length of the immediate control period and the frequency of visits during it; 5) dosage of the drug, length of time it was given and frequency of visits; 6) length of time and how frequently the patient was followed after stopping the drug; 7) the method of taking the blood pressures, and 8) the average blood pressure during the control period, during therapy and during the post-treatment period. It seems only by such presentation that the results of any clinical study of this baffling therapeutic problem permit scientific evaluation.

Palmer (*87, 88*) has also been impressed by the factor of mental stress in essential hypertension and the efficacy of medical treatment. He feels that careful and thorough medical treatment of essential hypertension results in a substantial fall in the systolic blood pressure in half of the mild and moderate cases and one-third of the severe cases. Symptomatic relief is obtained in 90 per cent of the mild cases, 75 per cent of the moderate cases and 46 per cent of the severe cases.

Robinson (*96*) reports a case of hypertension with an almost sudden disappearance of symptoms when the patient was relieved of emotional strain but without any change in the elevated blood pressure. Even shortness of breath on effort, which was thought to be due to the organic condition, disappeared suggesting that dyspnea was of psychogenic origin. He calls attention to the value of looking for psychic influences in the production of symptoms even when there may seem to be a satisfactory explanation for them in the existing organic disease.

Buck (*15*) reports on "the class method in the treatment of essential hypertension" from Pratt's Clinic where they depend upon the giving of testimony by older members of the class, explanation of the pathological physiology of the hypertension and the fact that the symptoms of early hypertension are psychic in origin. He states "some of our patients have shown no striking change in the level of their blood pressures, but in two-thirds of those who have made three or more visits to the class a fall in pressure of from 18–46 mm. of mercury has been observed". He goes on to say "our aim is not, however, primarily to reduce blood pressure, it is rather to aid these patients to obtain an optimal level of well being. The approach is frankly largely psychologic".

When we inquire into the usual medical management, however, we find

that rest and reassurance are the factors that are stressed. But a patient cannot be reassured about his condition if his attention is constantly focused on his blood pressure and he certainly cannot rest if he is preoccupied with ideas of a stroke, heart failure and kidney disease. A recent summary by Stewart (*108*) emphasizes the psychological approach. Even though Stewart's psychotherapy may be criticized as superficial he is to be commended for his efforts to treat the patient rather than the blood pressure. In common with the generally unfortunate attitude of medicine toward psychiatry it is stated that "it is harmful to send such patients to psychiatrists because of the implications of psychiatric care."

More adequate studies of the emotional lives of patients with hypertension have been published by Dunbar (*33*) and Wolfe (*119*).

They call attention to the increased tension and sometimes spasm of voluntary or smooth muscles or both that may be alleviated as unconscious conflicts become conscious. They feel that this tension is part of the whole defense mechanism, psychologically and physiologically a general attitude of being on guard. Often its significance is elaborated in terms of accompanying disturbance of tonus in other systems, especially in the gastrointestinal and the genito-urinary tract. They find that the hostile impulses against which the patient is on guard are usually relatively near the surface and accessible to treatment. As these impulses emerge to consciousness there is usually a rise in the blood pressure curve followed by a drop to a lower level as the material is worked through. There are usually transitory psychoneurotic manifestations of a phobic or compulsive nature in the course of such treatment. Dunbar, in addition to the studies just mentioned, as well as others (*34*, *35*), has dealt with the subject in detail in her comprehensive book on *Emotions and Bodily Changes* (*36*) in which among the many studies reported considerable attention is given to the opinions of Fahrenkamp whose psychophysical studies on hypertension are noteworthy. Fahrenkamp (*39*) feels that psychic factors play a decisive rôle in regard to the blood pressure level in all stages of the disorder and therefore that in all hypertensive patients the major emphasis should be on the treatment of the psychic element. However, it is impressive that this psychologically-minded physician does not accept the existence of a functional hypertension of purely psychogenic origin, since he has never seen a patient who completely lost his hypertension. In other words, in his experience the tendency of the circulatory system to pathological reaction remains demonstrable.

Elsewhere in this symposium psychoanalytical studies of hypertensive patients are reported so that I shall not refer in detail to these matters even though they represent the most fundamental studies along psychological lines that we have had so far. Psychoanalytic observations (*2*, *66*, *80*, *81*) on hypertension patients show the necessity for a more adequate approach to their study than "are you worried about anything" and a more adequate treatment than "go home and take it easy". This kind of superficial psychotherapy, if it may be termed that, is in line with the kind of medical management that has been given to the unfortunate sufferer from essential hypertension in the past.

What has been done in an effort to reduce the blood pressure? Because of an ill-founded idea that protein was responsible for hypertension and kidney disease the patient was denied meat and eggs, and especially red meat, which for some reason was looked upon

with particular dread. His diet was rendered even more unpalatable by the withdrawal of salt. Sympathy would doubtless have been extended to this half-starved fellow except that he probably was not able to eat anyway, his teeth having been extracted on the theory that focal infection had something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses punctured because of the same theory. In case some food had been consumed, the slight colonic residue was promptly washed out by numerous colonic irrigations, especially during the period when the theory of auto-intoxication was enjoying a wave of popularity. To add to his unhappiness he was often told to stop work and exercise. Of course, he was denied alcohol and tobacco as well as coffee and tea, and as a climax to the difficulties of this unfortunate person, he may now fall into the clutches of the neurosurgeon, who is prepared to separate him from his sympathetic nervous system.

This kind of an approach has grown out of our pernicious emphasis on "bringing the blood pressure down" to the exclusion of the much more fundamental understanding of the individual (*115*). It is freely admitted that the height of the blood pressure is one of the best indices to the condition and prognosis of the patient with essential hypertension but to put all of our attention on the matter of bringing this blood pressure down is to do the patient incalculable harm. I say this whether or not psychic factors are fundamental in hypertension.

We must redefine our objectives in the treatment of hypertension. The consideration of pathogenesis must impress us with the necessity for the total evaluation of the patient with hypertension. This will represent a combined physical and psychological study. When we do such a study we will realize that many symptoms occurring in hypertension are of emotional rather than physical origin and that incapacity is often out of proportion to the disease (*116*). Hence the importance in a great many patients of reeducation along the lines of "carrying on" rather than urging rest and more rest. Menninger (*80*) champions this idea on the basis that self-directed aggression may be turned outward by the authority of the physician and that extroversion of the aggression if not too strenuous may be of advantage to the patient. I have repeatedly proved this to my own satisfaction in patients who have been invalided by the knowledge of blood pressure rather than by the physical effects of hypertension.

The knowledge that "every psychic tendency seeks adequate bodily expression" (*2*) gives a practical hint in dealing with hypertension patients. Even though it may be questioned scientifically, an explanation to the effect that inner tension which cannot be released through ordinary channels may manifest itself in the circulatory system by hypertension, represents a rational approach as far as the patient is concerned; and often leads to a discussion of problems which are of considerable concern and importance from the standpoint of the illness.

To advise the individual involved in mental conflict not to worry is absurd especially when, as is so often the case, no concerted effort is made to find out what is disturbing him. Too often the physician is satisfied that there are no problems disturbing the patient after he has inquired, "Are you worried about anything?" and has received a negative reply. Most of the time the patient really does not know just how much he is disturbed nor does he relate the factors actually responsible for his discontent. He is much more apt to project his worries into questions about his blood pressure, heart, brain, and kid-

neys. Careful inquiry will bring out that his fears are exaggerated and that the reasons he assigns for them are illogical. There is only one approach that has any merit, that is, to encourage the patient to talk about himself as a person rather than as a medical case. This will permit some insight into conflict situations and lead often to some relief of anxiety, which is closely related to the high blood pressure. Although this approach does not offer a complete solution of the hypertensive problem and does not even apply to all patients, it is a practical method of dealing with a set of important factors that may be modified, whereas the constitution of the individual cannot be touched. It is an approach heretofore not sufficiently practiced. We are too much concerned with physical measurements in hypertension —the blood pressure figures, the percentage of renal function, the size of the heart, the electrocardiographic tracing, the amount of retinal sclerosis —all of which are essential in the study of the hypertensive person but give incomplete information from the standpoint of the total evaluation of the patient. They should represent the beginning and not the end of study. We are too little concerned with the emotional life, which may hold the key to the satisfactory management of the hypertensive patient.

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FRUSTRATION AS AN EXPERIMENTAL PROBLEM*

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IN OPENING THIS SYMPOSIUM Dr. Rosenzweig of the Worcester State Hospital pointed out the significance of frustration as a problem of research. The meaning of frustration, both operationally and theoretically, as related to such concepts as maladaptation, tension, and disturbances of homeostatis, and the implications of American functional psychology and psychoanalytic theory for systematic research upon frustration were discussed.

In his contribution Dr. Mowrer of Yale University dealt with some research potentialities of the frustration concept as related to social and educational problems. Attention was directed to 1) the importance of increasing the child's capacity to tolerate frustration in the interests of its own higher development, and to 2) the social implications of frustration in the interests of group harmony and stability. Both parts of the discussion included a series of relevant problems available for research.

Dr. Haslerud of the University of Tennessee, who has been conducting his studies at the Yale Laboratory of Primate Biology in Orange Park, Florida, carried the program forward with a paper on some interrelations of behavioral measures of frustration in chimpanzees. In his investigation some ten animals, six adult and four child chimpanzees, were first trained to expect food as a reward after pulling on a belt for a certain length of time. The food was offered to the animal in a tin container clipped on the belt by the experimenter behind the curtain concealing the wheel on which the belt was mounted. Frustration was induced in several ways, *e.g.*, by presenting the animal with an empty food container after a standard amount of work had been performed, or by locking the machine so that pulling on the belt no longer entailed any motion. Measurements of reaction to frustration were taken by rating emotional behavior, such as outbursts of anger or whimpering, and by noting any hesitation of the animal to proceed with a new trial after frustration. The time spent by the animal upon trials following frustrated attempts was also taken. The results of the experiments indicate that the type of frustrating situation plays a significant part in determining the reaction of the animal. For example, interrupted pull frustration gives more pronounced effects than the disappointment of finding an empty food container. However, the various measures of frustration are not highly correlated with each other. The animals were found to vary in their resistance to, or tolerance for, frustration, the

* [Abstract of a symposium at the annual meeting of the American Psychological Association, Columbus, Ohio, September 8, 1938. Participants: Saul Rosenzweig, Chairman; O. H. Mowrer, George M. Haslerud, Quin F. Curtis and Roger G. Barker. Discussants: Stuart W. Cook, James H. Elder, J. McV. Hunt and B. F. Skinner.]

child chimpanzee being much less resistant than the adult.

In the next paper Dr. Curtis of Ohio State University, who has worked on the problem of experimental neuroses at the Cornell Laboratory of physiology, discussed certain physiological consequences of frustration. A brief description of the classical Pavlovian technique for inducing behavior disorders in dogs experimentally was followed by an account of the extensions and modifications of the procedure by Liddell and his associates in their work with sheep and swine. Three characteristics of the neurosis are the permanence of the changes, their newness, and the fact that these alterations involve not only overt adjustments to the environment but the homeostatic physiological relationships as well. The last set of changes includes the intrinsic functions of respiration and heart action, both of which are significantly different in neurotic and normal animals. The possibility of using drugs to modify the disorder received mention.

Dr. Barker of the University of Illinois, who has performed experiments on frustration in children both with Kurt Lewin and at the Harvard Psychological Clinic, offered a contribution dealing with the effect of frustration on cognitive ability. The experimental procedure upon which his conclusions were based consisted in allowing children to play in a satisfying situation with many attractive toys on one occasion and then frustrating them by bringing them into the same play room but offering them considerably less attractive toys, the original toys being unattainable though still visible through a barrier of wire netting. The discussion of the effects of such frustration upon changes, whether towards increase or decrease, in cognitive ability was couched in the theoretical terms of a psychology which posits an inner system of psychological needs and an outer surrounding system comprising the perceptual, cognitive, and motor functions. The conclusion was drawn from the experiments and theoretical analysis that intellectual ability varies with the psychological situation of the individual and that such information is highly important for completing our understanding of individual (statistical) differences in intelligence.

Dr. Rosenzweig in conclusion presented a general analysis of frustration to integrate in some measure what had been said by the various speakers with work previously performed and possibilities for further studies in the field of frustration. The treatment included a delineation of types of frustrating situations—privations, deprivations and conflicts, either external or internal to the organism in point of origin. A concept centering around the individual's capacity to withstand frustration without resorting to inadequate modes of reaction was introduced and designated frustration tolerance. The relations of this concept to problems of education and re-education were pointed out. Finally, certain types of reaction to frustration were discussed from the point of view of their adequacy, directness (substitute character), defensive or preservative rôle in the economy of the organism, and their specificity as related to psychological dynamics. Attention was called to the possible fruitfulness of the work represented in the symposium for a rapprochement between psychoanalysis and experimental psychology, and for a reduction of the differences now separating normal and abnormal psychology, and abnormal psychology and theoretical psychiatry.

An extended account of the symposium may be found in *Character and Personality* for December, 1938.